PATIENT

DISEASE Colon adenocarcinoma (CRC)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
KRAS wildtype (codons 12 & 13)	Erbitux® (Cetuximab)
KRAS/NRAS wildtype (codons 12, 13, 59, 61, 117, & 146 in exons 2, 3, & 4)	Vectibix® (Panitumumab)

For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be performed.

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MSI-High §
Tumor Mutational Burden 35 Muts/Mb §
ASXL1 G645fs*58
ASXL1 S1335fs*115
ATM R3047*
BAP1 I191fs*2
CDH1 P127fs*41
CDH1 S70fs*13
CIC P1597fs*23
CTNNB1 W383R
FAM123B E370fs*8
MLL2 P2354fs*30
NTRK1 TPM3(NM_152263)-NTRK1(NM_002529) fusion (T10*; N9) §
PALB2 M296fs*1
RNF43 G659fs*41
SUFU A25fs*23
TP53 R273C

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Note: The intended use (IU) statement and claims made on this sample report may not be up to date. For the latest version of the FoundationOne CDx claims and IU, please see the current label: www.foundationmedicine.com/f1cdx

ABOUT THE TEST FoundationOne®CDx is the first FDA-approved broad companion diagnostic for solid tumors.

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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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) and tumor mutational burden (TMB) 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 the targeted therapies listed in Table 1 in accordance with the 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. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

The test is also used for detection of genomic loss of heterozygosity (LOH) from FFPE ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the RUBRACA product label.

The F1CDx assay will be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E and V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)

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Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

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Biomarker Findings

Microsatellite status - MSI-High
Tumor Mutational Burden - 35 Muts/Mb

Genomic Findings

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

KRAS wildtype
NRAS wildtype
NTRK1 TPM3-NTRK1 fusion
ATM R3047*
PALB2 M296fs*1
CTNNB1 W383R
RNF43 G659fs*41
SUFU A25fs*23
ASXL1 G645fs*58, S1335fs*115
BAP1 I191fs*2
CDH1 S70fs*13, P127fs*41
CIC P1597fs*23
FAM123B E370fs*8
MLL2 P2354fs*30
TP53 R273C

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

15 Therapies with Clinical Benefit
0 Therapies with Lack of Response
47 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Microsatellite status - MSI-High	Nivolumab 2A	Atezolizumab
	Pembrolizumab 2A	Avelumab
		Cemiplimab
10 Trials *see p. 19*		Durvalumab
Tumor Mutational Burden - 35 Muts/Mb	Nivolumab	Atezolizumab
	Pembrolizumab	Avelumab
		Cemiplimab
10 Trials *see p. 21*		Durvalumab

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
KRAS - wildtype	Cetuximab 2A	none
0 Trials	Panitumumab 2A	
NRAS - wildtype	Cetuximab 2A	none
0 Trials	Panitumumab 2A	
NTRK1 - TPM3-NTRK1 fusion	Entrectinib 2A	Crizotinib
6 Trials *see p. 27*	Larotrectinib 2A	
ATM - R3047*	none	Niraparib
		Olaparib
		Rucaparib
10 Trials *see p. 23*		Talazoparib
PALB2 - M296fs*1	none	Niraparib
		Olaparib
		Rucaparib
10 Trials *see p. 28*		Talazoparib
CTNNB1 - W383R	none	none
10 Trials *see p. 25*		
RNF43 - G659fs*41	none	none
2 Trials *see p. 30*		
SUFU - A25fs*23	none	none
5 Trials *see p. 31*		

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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.

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BIOMARKER

Microsatellite status

RESULT
MSI-High

POTENTIAL TREATMENT STRATEGIES

On the basis of prospective clinical evidence in multiple solid tumor types, MSI and associated increased mutational burden[1-2] may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors[2-6], including the approved therapies nivolumab[7-8], pembrolizumab[9-10], atezolizumab, avelumab, and durvalumab[3-5] . Pembrolizumab therapy resulted in a significantly higher objective response rate in MSI-H CRC compared with MSS CRC (40% vs. 0%)[9]. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with tumors with high MSI than those without[7]. An earlier case study reported that nivolumab therapy resulted in a complete response in a patient with MSI-H CRC[8]. A Phase 1b trial of atezolizumab combined with bevacizumab reported PRs for 40% (4/10) of patients with MSI-H CRC[3]. MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX[11-12] and FOLFIRI[13-14]. MSI and deficient MMR are associated with lack of benefit of postsurgical fluorouracil (FU)-based adjuvant therapy[15-16] but may predict benefit from irinotecan chemotherapy[17].

FREQUENCY & PROGNOSIS

MSI-H colorectal cancers (CRCs) make up 10-15% of CRC cases[2,18-21]. Multiple studies have shown that MSI-H CRCs have a better prognosis than MSI-low (MSI-L) or microsatellite stable (MSS) tumors[18,22-28]. MSI-H CRCs are associated with certain pathologic and molecular features, including poor differentiation, right-sided and mucinous tumors, increased numbers of tumor infiltrating lymphocytes, diploidy, and a relatively high frequency of BRAF mutations[19-20,29].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[20]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[20,30-31]. This sample has a high level of MSI, equivalent to the clinical definition of an MSI-high (MSI-H) tumor: one with mutations in >30% of microsatellite markers[19,29,32]. MSI-H status indicates high-level deficiency in MMR and typically correlates with loss of expression of at least one, and often two, MMR family proteins[19-20,29,31]. While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[20], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[33]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[33-35] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[36-38]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
35 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[39-41] and anti-PD-1 therapies[39-42]. A large-scale retrospective analysis of immune checkpoint inhibitor efficacy in CRC reported significantly improved OS for patients with tumors harboring TMB ≥ 12 Muts/Mb compared to those with tumors with TMB < 12 Muts/Mb[39]. Another 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[43].

FREQUENCY & PROGNOSIS

Elevated TMB has been reported in 8-25% of colorectal cancer (CRC) samples[21,44-46]. 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)[21,46]. 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[44-46]. 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[21,46]. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB[21,46], whereas TMB-low tumors more frequently harbor mutations in TP53 and APC[21]. Although direct associations between blood or tissue TMB and prognosis of patients with CRC have not been reported, multiple studies have shown that MSI-H CRCs have a better prognosis than MSI-low (MSI-L) or microsatellite stable (MSS) tumors[18,22-28].

FINDING SUMMARY

Tumor mutational 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[10,49], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[21,50-53], and microsatellite instability (MSI)[21,50,53]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[39,43].

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GENE
KRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES
Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[54-57] or panitumumab[58-60] in patients with CRC. Therefore, these agents are indicated for treatment of patients with CRC lacking such mutations (NCCN Guidelines v2.2019).

FREQUENCY & PROGNOSIS
Approximately 50-65% of colorectal cancers (CRCs) have been reported to lack KRAS mutations[61-69]. Numerous studies have reported that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC[63-66,70-71].

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[72-73]. No alterations in KRAS were identified in this case.

GENE
NRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES
Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[54-57] or panitumumab[58-60] in patients with CRC. Therefore, these agents are indicated for treatment of patients with CRC lacking such mutations (NCCN Guidelines v2.2019).

FREQUENCY & PROGNOSIS
The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[21,69,74-79]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[69] and longer survival[79-80] 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[72]. No alterations in NRAS were identified in this case.

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GENE
NTRK1

ALTERATION
TPM3-NTRK1 fusion

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data indicate that NTRK fusions predict sensitivity to TRK inhibitors such as larotrectinib, entrectinib, AZD7451, belizatinib, and PLX7486[81-91]. Durable clinical responses have also been reported in patients with NTRK1 fusion-positive tumors treated with the mutikinase inhibitor crizotinib[82,85-86,92-94]. Larotrectinib is approved to treat patients with NTRK fusion-positive solid tumors based on ORR and duration of response. Analysis of combined data from several larotrectinib studies reported an ORR of 81% (88/109) in adult and pediatric patients with various solid tumors harboring NTRK fusions treated with larotrectinib; the responses were durable, and CRs was were observed in 17% of patients[90]. In a Phase 1/2 study of patients with NTRK fusions, larotrectinib showed clinical efficacy in cancers with intracranial disease; disease control was observed in all evaluable patients (1 PR, 7 SDs) with primary CNS tumors[95]. Pooled analysis of 3 Phase 1/2 trials of entrectinib for adult patients with NTRK fusion-positive solid tumors reported an ORR of 57% (31/54), a median PFS of 11.2 months, and a median OS of 20.9 months[96-97] . Similar activity was observed for patients with NTRK1 fusions (ORR of 59% [13/22]) and NTRK3 fusions (ORR of 58% [18/31]); however, 1 patient with NTRK2 fusion did not respond[96]. Subgroup analysis of patients with NSCLC reported an ORR of 70% with intracranial response seen in 4 out of 6 patients[97]. A Phase 1/1B trial of entrectinib for children and adolescents with recurrent or refractory solid tumors reported a CR in a patient with high-grade glioma (HGG) and an NTRK3 fusion, 2 PRs in patients with HGG and NTRK1 and NTRK2 fusions, 2 PRs in patients with infantile fibrosarcoma (IFS) and NTRK3 fusions, and 1 PR in a patient with melanoma and an NTRK3 fusion[98]. Acquired resistance to larotrectinib and entrectinib due to the emergence of kinase domain mutations in NTRK fusions has been reported in some patients[89-90,99-100]. Next-generation TRK inhibitors such as selitrectinib (LOXO-195) and repotrectinib have shown preclinical and clinical activity against acquired NTRK resistance mutations[99,101-102]. In patients with NTRK fusion-positive cancers previously treated with at least 1 prior TRK inhibitor, treatment with selitrectinib achieved an ORR of 34% (10/29) with an ORR of 45% (9/20) in patients harboring a TRK kinase mutation[103]. Analysis of paired pre- and post-treatment samples from patients with NTRK1 or NTRK3 fusions treated with various first or next generation TRK inhibitors, identified emerging mutations in the MAPK or upstream RTK pathway (BRAF, KRAS, MET, MAP2K1) in 6/8 patients who developed acquired resistance[104]. Limited clinical and preclinical data suggest upfront combination TRK and MEK inhibitor treatment may be more effective than sequential treatment[104].

FREQUENCY & PROGNOSIS

In the TCGA dataset, NTRK1 mutation was observed in 2% of colorectal adenocarcinoma cases and NTRK1 amplification was observed in fewer than 1% of cases[21]. NTRK1 fusions have been reported in 1.4% (1/70) to 8.3% (1/12) of colorectal cancer (CRC) cases; the most common fusion partner in these cases is TPM3, but fusions involving LMNA have also been reported[94,105-110]. The presence of an NTRK1-involving fusion has been positively correlated with TRKA protein expression in CRC[94,105,107]. In one study, the presence of an ALK, ROS1, NTRK1 or NTRK3 rearrangement correlated with inferior survival for patients with CRC, including no responses to cetuximab or panitumumab by any of the four treated patients[111]. One study reported TRKA protein expression in CRC to associate with a slight but significantly shorter patient survival (P = 0.0411, hazard ratio = 0.5346)[94].

FINDING SUMMARY

NTRK1 encodes the receptor tyrosine kinase TRKA, which plays a role in the development of the nervous system by regulating cell proliferation, differentiation, and survival of neurons. TRKA is activated upon binding of its ligand NGF to promote several downstream signaling pathways including GRB2-RAS-MAPK, NF-Kappa-B, and RAS-PI3K-AKT1[112-115]. NTRK1 fusions that include an N-terminal oligomerization-promoting partner gene linked to the kinase domain of TRKA (aa 510-781), as seen here, have been characterized as activating, exhibiting constitutive kinase activity and tyrosine phosphorylation[82-83,108,116-120]. Patients with NTRK1 fusions have experienced clinical benefit from TRK inhibitors such as larotrectinib[90-91] and entrectinib[89] and from crizotinib[82,85,92].

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GENE
ATM

ALTERATION
R3047*

TRANSCRIPT NUMBER
NM_000051

CODING SEQUENCE EFFECT
9139C>T

POTENTIAL TREATMENT STRATEGIES

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[121] and ATR inhibitors. In a Phase 2 trial, 4 out of 5 patients with ATM-mutated castration-resistant prostate cancer benefited from olaparib treatment[122]. In a Phase 2 study of patients with gastric cancer, the combination of olaparib with paclitaxel resulted in improved OS versus paclitaxel alone, both in the overall patient population and the patient population with low ATM protein expression[123]. Preclinical studies have generally shown that loss of functional ATM confers moderate sensitivity to PARP inhibitors[124-131]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with CRC who achieved a CR to berzosertib[132] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[133] harbored ATM inactivation or protein loss; preclinical studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[134-136] and hematologic malignancies[134,137] 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[138].

FREQUENCY & PROGNOSIS

In the Colorectal Adenocarcinoma TCGA dataset, ATM mutations have been reported in 11% of cases[21]. Loss of heterozygosity (LOH) of ATM has been observed in 23-31% of distal colon cancers, but not in proximal colon tumors[139]. ATM expression or mutation has been associated with longer survival for patients with CRC[140-141].

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[142]. Loss of functional ATM promotes tumorigenesis[143] and mutations in ATM underlie the rare autosomal recessive inherited disorder ataxia-telangiectasia that is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[142]. ATM mutations that disrupt the TP53 binding site (amino acids 60-130), protein kinase domain (amino acids 2712-2962) or FATC domain (amino acids 3024-3056), such as observed here, are predicted to result in loss of function[144-146].

GENE
PALB2

ALTERATION
M296fs*1

TRANSCRIPT NUMBER
NM_024675

CODING SEQUENCE EFFECT
886delA

POTENTIAL TREATMENT STRATEGIES

Emerging clinical[122,147] and strong preclinical[148-150] evidence indicates that loss or inactivation of PALB2 may confer sensitivity to PARP inhibitors, such as olaparib, rucaparib, and niraparib. Inactivation of the Fanconi anemia/BRCA pathway, including PALB2 mutations, also sensitizes cells to mitomycin C and cisplatin[148,151-153].

FREQUENCY & PROGNOSIS

PALB2 mutation has been detected in 3% of colorectal adenocarcinoma (CRC) cases[106]. In one study, somatic mutations in PALB2 were reported in 2.5% (1/40) of MSI-high but none (0/15) of the MSI low CRC samples analyzed[154]. Although the prognostic significance of PALB2 mutation in CRC is not clear, several studies have suggested that germline PALB2 mutations are associated with increased risk of late-onset CRC[155-157].

FINDING SUMMARY

PALB2, also known as FANCN (Fanconi Anemia complementation group N), encodes a BRCA2-binding protein that acts to stabilize the association of BRCA2 with chromatin and the nuclear matrix[158]. The PALB2 protein additionally acts to functionally connect BRCA1 and BRCA2 with one another in response to DNA damage; cells with defective PALB2 are deficient in the homologous recombination repair response to double-strand DNA breaks[158-161]. PALB2 alterations that disrupt domains required for BRCA1 or BRCA2 association and homologous recombination, including the coiled-coil (amino acids 1-71) or WD40 domains (amino acids 854-1186), such as observed here, are predicted to be inactivating[159-160]. Inactivating germline mutations in PALB2 have been associated with increased risk of breast cancer, with a cumulative risk estimated at 35% to 40% by age 70[162-164], as well as with elevated risk of pancreatic and ovarian cancer development[165]. Biallelic mutations of PALB2 are associated with Fanconi anemia (FA), a rare autosomal recessive disorder that predisposes patients to a subset of cancers, including acute myeloid leukemia (AML), myelodysplastic syndrome, gynecological malignancies, and head and neck tumors[166-168]; frequency estimates suggest an incidence of 3:1,000,000 individuals in Europe and the US, and a heterozygous carrier frequency of 1:181 and 1:300 in the US and Europe, respectively, with slightly higher rates in some groups, such as the Ashkenazi Jewish population (1:89)[167,169]. In the appropriate clinical context, germline testing of PALB2 is recommended.

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GENE
CTNNB1

ALTERATION
W383R

TRANSCRIPT NUMBER
NM_001904

CODING SEQUENCE EFFECT
1147T>C

POTENTIAL TREATMENT STRATEGIES

Mutation or activation of CTNNB1 signaling has been shown to increase mTOR signaling, promote tumorigenesis, and respond to mTOR inhibition in preclinical studies[170-172]. The mTOR inhibitors everolimus and temsirolimus have shown clinical activity in patients with endometrial carcinoma and CTNNB1 mutations[173-174]. A patient with recurrent hepatocellular carcinoma and a CTNNB1 mutation, who had progressed on sorafenib monotherapy, experienced tumor regression and clinical benefit upon combination treatment with everolimus and sorafenib[175]. In preclinical studies, CTNNB1 activating mutations have been shown to increase expression of WNT pathway member DKK1, which may promote tumor cell proliferation and immune evasion[176-178]. A Phase 1 trial of DKK1-targeting antibody DKN-01 in combination with paclitaxel in esophageal cancer reported a PR rate of 50% (2/4 patients) and SD rate of 25% (1/4) in patients with CTNNB1 activating mutations, compared with 24% (10/41) PR and 37% (15/41) SD in unselected patients[179]. Multiple preclinical studies in cancer models harboring CTNNB1 mutation or beta-catenin pathway activation have reported activation of the NOTCH pathway and sensitivity to pharmacologic inhibition of NOTCH signaling by gamma-secretase inhibitors[180-183]. Phase 1 and 2 clinical trials of gamma-secretase inhibitor PF-03084014 have shown high response rates in patients with desmoid tumors, which are driven by activating CTNNB1 mutations in the majority of cases[184-185], suggesting CTNNB1-mutant tumors may be sensitive to gamma-secretase inhibitors. Although WNT pathway inhibitors have been explored preclinically in CTNNB1-mutant cells, clinical data supporting this therapeutic approach are lacking[171,186-188]. Multiple clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies to treat colorectal cancer (CRC), even for tumors that harbor alterations in PIK3CA, AKT, and/or PTEN[189-195]. One patient with CRC harboring an AKT1 E17K mutation experienced short-term stable disease on monotherapy treatment with the AKT inhibitor AZD5363[195]. Resistance to therapy may arise, at least in part, through activation of the RAS-MAPK pathway[190-192]. Combinations of therapies may be required to overcome this lack of response, as demonstrated by both clinical and preclinical studies evaluating the efficacy of PI3K-AKT-mTOR pathway inhibitors in combination with chemotherapy[196] or inhibitors of the VEGF signaling pathway[197-198]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

CTNNB1 mutations have been reported in 5-7% of colorectal adenocarcinomas[21,106,199]. Overexpression of beta-catenin has been observed in up to 80% of colorectal tumors, resulting in activation of the WNT/beta-catenin pathway[200-202]. Findings concerning the association between beta-catenin expression and prognosis in patients with colorectal cancer have been conflicting, with some studies correlating expression with better overall survival and other studies associating beta-catenin expression with poor overall survival[200,203-205].

FINDING SUMMARY

CTNNB1 encodes beta-catenin, a key downstream component of the WNT signaling pathway. Beta-catenin interacts with cadherin to regulate cell-cell adhesion; as a component of the WNT pathway, it also plays a role in development, cell proliferation, and cell differentiation[206]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
RNF43

ALTERATION
G659fs*41

TRANSCRIPT NUMBER
NM_017763

CODING SEQUENCE EFFECT
1976delG

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[207-211]. 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[212-213], 3-5% of pancreatic cancers[214], 21% of ovarian mucinous carcinomas[215], 9% of liver fluke-associated cholangiocarcinomas[216], and up to 18% of colorectal cancers[21,213]. RNF43 mutations are associated with mismatch repair deficiency and microsatellite instability (MSI) in colorectal[213], endometrial[213], and gastric cancers[217-218]; one study reported RNF43 alterations in more than 50% of MSI gastric carcinomas[217].

FINDING SUMMARY

RNF43 encodes a ubiquitin ligase[219] that was discovered because it is overexpressed in colon cancer[220]. RNF43 and the homologous E3 ubiquitin ligase ZNRF3 are tumor suppressors that function as negative regulators of WNT signaling[207-211]. 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[221].

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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GENE
SUFU

ALTERATION
A25fs*23

TRANSCRIPT NUMBER
NM_016169

CODING SEQUENCE EFFECT
71_72insC

POTENTIAL TREATMENT STRATEGIES

Although SUFU leads to activated Hedgehog signaling[222], clinical and preclinical studies have shown that SMO inhibitors that target upstream Hedgehog signaling, such as sonidegib and vismodegib, are ineffective in cancers with alterations that inactivate SUFU[223-224]. Therapies targeting the Hh pathway downstream of SUFU are under investigation and may be appropriate for patients with SUFU mutation[222]. Arsenic trioxide has been reported to inhibit GLI transcription factors[225-227], and other Hh pathway inhibitors that act downstream of SUFU are under investigation[228-229]. The transcriptional activity of the GLI transcription factors have been shown to be dependent on the bromo and extra C-terminal (BET) bromodomain protein BRD4; preclinical studies have shown that the BET inhibitor JQ1 results in downregulation of GLI transcriptional activity in SUFU mutant cells and inhibits SUFU-mutant medulloblastoma cell growth in vitro and in vivo[230]. Therefore, BET inhibitors may be a relevant therapeutic approach for cancers with SUFU loss or inactivation. BET inhibitors are in clinical trials for multiple cancer types.

FREQUENCY & PROGNOSIS

In the TCGA Colorectal Adenocarcinoma dataset, SUFU mutation was found in 1% of cases and SUFU homozygous deletion was found in fewer than 1% of cases[21]. Increased SUFU mRNA and protein expression has been detected in colon cancer tissues, and expression correlated with tumor invasion[231].

FINDING SUMMARY

SUFU encodes a negative regulator of the Hedgehog signaling pathway that functions by sequestering and inactivating the GLI transcription factors[222]. SUFU is a tumor suppressor and germline loss-of-function mutations in SUFU are associated with pediatric medulloblastoma and meningioma[232-234]. Mice with loss of SUFU, along with p53 loss of function, develop medulloblastoma[235-236]. Alterations that disrupt the SUFU-GLI interaction[237-239], or are associated with SHH-subtype medulloblastoma[224] or childhood medulloblastoma[232,234,240], such as observed here, are predicted to result in increased GLI transcriptional activity.

GENE
ASXL1

ALTERATION
G645fs*58, S1335fs*115

TRANSCRIPT NUMBER
NM_015338

CODING SEQUENCE EFFECT
- 1934delG
- 3999delT

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies available to address genomic alterations in ASXL1.

FREQUENCY & PROGNOSIS

ASXL1 mutations have been reported in various solid tumors, including 4% of colorectal cancers[199], 3% of breast cancers[241], 2% of hepatocellular carcinomas[242], 2% (1/61) of prostate cancers[243], and 1.4% (1/74) of head and neck squamous cell carcinomas[244]. ASXL1 amplification has also been reported in 5.1% of cervical cancers[245]. ASXL1 mutations have mainly been studied and reported in the context of hematological malignancies, where they have been correlated with poor prognosis in myelodysplastic syndromes, chronic myelomonocytic leukemia, acute myeloid leukemia, and myeloproliferative neoplasms[246-248]. ASXL1 mutations have been associated with clonal hematopoiesis of indeterminate potential (CHIP), which is age-related and associated with increased risk of hematologic cancers[249-253]; however, the role of ASXL1 alterations in solid tumors is unclear.

FINDING SUMMARY

ASXL1 (additional sex combs-like 1) encodes a chromatin-binding protein involved in transcriptional regulation through interaction with the polycomb complex proteins and various other transcriptional regulators[247,254]. Germline inactivating mutations affecting ASXL1 underlie the very rare developmental disorder Bohring-Opitz syndrome[255]. ASXL1 alterations that remove the PHD domain (amino acids 1491–1541), including truncating mutations and deletions, lead to aberrant epigenetic regulation[246,254,256].

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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GENE
BAP1

ALTERATION
I191fs*2

TRANSCRIPT NUMBER
NM_004656

CODING SEQUENCE EFFECT
570_571insC

POTENTIAL TREATMENT STRATEGIES

Clinical[257] and preclinical[258] evidence in the context of mesothelioma suggests that tumors with BAP1 inactivation may be sensitive to EZH2 inhibitors such as tazemetostat. Preclinical studies suggest that BAP1 is involved in the DNA damage response[259-262], and BAP1 inactivation might be associated with sensitivity to PARP inhibitors[260-261]. One preclinical study suggests that HDAC inhibitors may be beneficial in BAP1-mutated uveal melanoma; however, it is unclear if these inhibitors are effective in other BAP1-mutated cancers[263]. HDAC inhibitors, such as belinostat and vorinostat, are in clinical trials in solid tumors.

FREQUENCY & PROGNOSIS

BAP1 loss and mutation have been reported in 0.9% and 0.9-2.2% of colorectal adenocarcinomas, respectively[21,106,199,264]. Decreases in the expression BAP1 mRNA and protein have been reported in colorectal cancers and have been associated with poor prognosis[265].

FINDING SUMMARY

BAP1 (BRCA1 associated protein-1) encodes a ubiquitin hydrolase, a protein involved in regulating the availability of target proteins for the ubiquitin-proteasome protein degradation pathway; BAP1 is located on chromosome 3p21.3, in a region of frequent loss of heterozygosity (LOH) in breast and lung cancer, and has been postulated to be a tumor suppressor[266-267]. BAP1 alterations that disrupt the ubiquitin C-terminal hydrolase domain (amino acids 1-240) and/or the nuclear localization signal (amino acids 717-722), such as observed here, are predicted to be inactivating[267-268]. Germline inactivating mutations in BAP1 have been associated with predisposition to several cancers, including renal carcinoma, mesothelioma, uveal melanoma, and melanocytic tumors[269-273].

GENE
CDH1

ALTERATION
S70fs*13, P127fs*41

TRANSCRIPT NUMBER
NM_004360

CODING SEQUENCE EFFECT
- 208delT
- 377_378insC

POTENTIAL TREATMENT STRATEGIES

There are no available therapies to compensate directly for CDH1 mutation or loss or for E-cadherin inactivation.

FREQUENCY & PROGNOSIS

In the TCGA datasets, CDH1 mutation has been most frequently observed in breast invasive carcinoma (13.4%)[274], stomach adenocarcinoma (10%)[218], and endometrial carcinoma (5.2%)[50]. Truncating somatic alterations in the CDH1 gene have also been reported in 84% (26/31) of plasmacytoid bladder cancer cases but not in any cases with non-plasmacytoid histology (0/56)[275]. CDH1 homozygous deletion has been reported at the highest incidence in prostate adenocarcinoma (4.5%)[276] and ovarian serous cystadenocarcinoma (2.5%)[277]. Loss of heterozygosity (LOH) of the CDH1 locus was found in gallbladder cancer[278], gastric cancer[279], endometrial carcinoma[280], and meningioma[281]. CDH1 inactivation, through mutations, reduced or lost expression, or promoter hypermethylation, has been associated with more advanced tumor stage, poor prognosis or reduced overall survival in a number of solid tumors, including breast cancer[282-284], endometrial cancer[285-286], gastric cancer[279], non-small cell lung carcinoma[287], ovarian carcinoma[288], pancreatic adenocarcinoma[289], colon cancer[290-291], cervical squamous cell carcinoma[292], cholangiocarcinoma[293-294], head and neck cancer squamous cell carcinoma (HNSCC)[295-296], and early stage esophageal squamous cell carcinoma[297].

FINDING SUMMARY

CDH1 encodes the transmembrane protein E-cadherin, a tumor suppressor that plays an important role in epithelial cell-cell adhesion and tissue morphogenesis[298]. Loss of E-cadherin expression leads to decreased cellular adhesion and results in cell migration and cancer metastasis[299-302]. CDH1 alterations that remove or disrupt critical domains of E-cadherin, including the extracellular cadherin (amino acids 155-709), juxtamembrane (amino acids 734-783), and catenin binding (amino acids 811-882) domains, are predicted to be inactivating[303-307]. Germline CDH1 mutations, including truncations, splice site mutations, and missense mutations, have been reported in patients with hereditary diffuse gastric cancer[308] and infiltrating lobular breast cancer[309-310].

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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GENE
CIC

ALTERATION
P1597fs*23

TRANSCRIPT NUMBER
NM_015125

CODING SEQUENCE EFFECT
4790delC

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in CIC. One study reported MYC expression in all tested CIC-DUX4 and CIC-DUX4L sarcomas, with MYC amplification in the majority of cases[311]. Another study found WT1 overexpression in all CIC-DUX4 tumors[312]. Strategies to target MYC overexpression include inhibition of CDK1, CDK2, Aurora kinase B, and BRD4[313-321]. WT1 overexpression may confer sensitivity to anti-WT1 peptide vaccines[322-326]. However, these approaches have not been tested in the context of CIC-DUX4/DUX4L fusions and it is not known if CIC fusions with partners other than DUX4 or DUX4L upregulate MYC or WT1.

FREQUENCY & PROGNOSIS
CIC mutations have also been described in various solid tumors, including 1-10% of sequenced gastric, endometrial, and colorectal carcinomas and melanoma tumors (COSMIC, cBioPortal, 2020), although the consequences of CIC mutations in these tumor types have not been studied. CIC mutations have been observed in 58-69% of oligodendrogliomas but are less common in other gliomas, such as astrocytoma or oligoastrocytoma[327-329]. Conflicting data have been reported regarding the prognostic significance of CIC mutation in oligodendroglioma[328,330-331]. CIC-DUX4 fusions and CIC-DUX4L fusions have been observed in small round cell sarcomas[332-334], and have been associated with aggressive disease[335]. The CIC-FOXO4 fusion has also been reported infrequently in Ewing-like and small round cell sarcomas[336-338].

FINDING SUMMARY
CIC encodes a transcriptional repressor that plays a role in central nervous system development[339] and is frequently inactivated in oligodendroglioma[327-328]. CIC fusions, such as CIC-DUX4 fusion and CIC-DUX4L fusion, have been demonstrated to be activating, leading to aberrant gene expression and cellular transformation[332-334].

GENE
FAM123B

ALTERATION
E370fs*8

TRANSCRIPT NUMBER
NM_152424

CODING SEQUENCE EFFECT
1108_1109insG

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in FAM123B.

FREQUENCY & PROGNOSIS
Somatic mutation of FAM123B is rare in most cancers (COSMIC, 2020), but is observed at rates ranging from 5-30% in Wilms tumor[340-342]. No association between FAM123B alteration and clinical features or outcomes of Wilms tumor has been documented.

FINDING SUMMARY
FAM123B, also known as AMER1, encodes the protein WTX, which binds to beta-catenin, enhancing its proteasomal degradation and thereby exerting a repressive effect on WNT pathway signaling[343]. Germline mutation or deletion of FAM123B causes osteopathia striata with cranial sclerosis[344-345].

GENE
MLL2

ALTERATION
P2354fs*30

TRANSCRIPT NUMBER
NM_003482

CODING SEQUENCE EFFECT
7061delC

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in MLL2.

FREQUENCY & PROGNOSIS
Somatic alterations of MLL2 are frequently observed in lymphoma, including in the majority of follicular lymphomas, where the observed pattern of genomic alterations suggests a tumor suppressor function[346]. MLL2 alterations are also observed in a number of solid tumor contexts (COSMIC, 2020), being especially prevalent in squamous cell lung carcinoma[347] and small cell lung carcinoma[348].

FINDING SUMMARY
MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[349]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[350].

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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GENE
TP53

ALTERATION
R273C

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
817C>T

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[351-354], or p53 gene therapy and immunotherapeutics such as SGT-53[355-359] and ALT-801[360]. 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[361]. 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[362]. 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[363]. 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[364]. 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[365]. 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[366]. 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[359]. 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[367]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[368-370]. In a Phase 1b trial in 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[371]. 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[137,372]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[373-374]. 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[21,375-380]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[381]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[382].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[383]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[384-386]. One or more of the TP53 variants observed here has been described in the ClinVar database as a pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with Li-Fraumeni syndrome (ClinVar, Nov 2019)[387]. 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[388-390], including sarcomas[391-392]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[393] to 1:20,000[392]. 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[394]. In the appropriate clinical context, germline testing of TP53 is recommended.

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Cetuximab

Assay findings association

KRAS
wildtype

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). Cetuximab is also approved for BRAF V600E-mutated CRC in combination with the BRAF inhibitor encorafenib. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including cetuximab, have been shown to have significant clinical activity in patients with CRC[54-57,395-396] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Guidelines v2.2019).

SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate in patients with KRAS wild-type CRC, both as first-line combination therapy with FOLFIRI or FOLFOX4[54-55,396] and as monotherapy or combination therapy with irinotecan for chemotherapy-refractory patients[56-57,395] . A study of first line cetuximab in 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[397]. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS/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%[398].

Entrectinib

Assay findings association

NTRK1
TPM3-NTRK1 fusion

AREAS OF THERAPEUTIC USE

Entrectinib is a TKI that targets TRKA/B/C (NTRK1/2/3), ROS1, and ALK. It is FDA approved to treat adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) and adult and pediatric patients with NTRK fusion-positive solid tumors that lack a known acquired resistance mutation and are metastatic or likely to result in severe morbidity after surgical resection, have no satisfactory alternative treatments, or have progressed following treatment.

GENE ASSOCIATION

Based on extensive clinical evidence in various solid tumor types[89,96,98,399] , NTRK fusions may predict sensitivity to entrectinib.

SUPPORTING DATA

Analysis of combined data from 3 Phase 1/2 trials of entrectinib (ALKA-372-001, STARTRK-1, and STARTRK-2) for adult patients with various NTRK fusion-positive solid tumors reported an ORR of 57.4% (31/54, 4 CRs), median PFS of 11.2 months, and median OS of 21 months; intracranial ORR was 54.5% (6/11)[400]. Additionally, 100% (6/6) of evaluable pediatric patients with high-grade glioma (n=3), melanoma (n=1), or infantile fibrosarcoma (n=2) with NTRK fusions responded to entrectinib[98]. Clinical benefit with entrectinib monotherapy has been achieved for adult and pediatric patients with various solid tumors with and without CNS metastases and with NTRK, ROS1, or ALK fusions[89,98,399,401-403] , and preclinical sensitivity has been observed in NTRK fusion-positive AML cell lines[404]. In a Phase 1 trial, responses were restricted to patients harboring NTRK, ROS1, or ALK rearrangements, with the exception of ALK-mutant neuroblastoma, and were observed for patients with ALK or ROS1 rearrangements who had not received prior ALK TKI or crizotinib, respectively[89].

Larotrectinib

Assay findings association

NTRK1
TPM3-NTRK1 fusion

AREAS OF THERAPEUTIC USE

Larotrectinib is a tyrosine kinase inhibitor that targets NTRK1, NTRK2, and NTRK3. It is FDA approved to treat adult and pediatric patients with NTRK fusion-positive solid tumors that lack a known acquired resistance mutation and are metastatic or likely to result in severe morbidity after surgical resection, and have no satisfactory alternative treatments, or that have progressed following treatment.

GENE ASSOCIATION

Based on extensive clinical evidence in various solid tumors[90-91,405] , NTRK fusions may predict sensitivity to larotrectinib.

SUPPORTING DATA

A Phase 2 larotrectinib trial reported a 25% ORR (1/4) for patients with NTRK-fusion-positive colorectal cancer[90]. Analysis of combined data from a Phase 1, Phase 1/2, and Phase 2 trials reported an ORR of 81% (88/109) in adult and pediatric patients with various solid tumors, including soft tissue sarcoma, salivary gland tumor, thyroid carcinoma, GIST, lung tumor, melanoma, and CRC harboring NTRK fusions treated with larotrectinib; CR was observed in 17% of patients[405]. At 12 months of treatment, responses were ongoing in 75-81% of patients[90,405] . Acquired resistance to larotrectinib, putatively due to detected kinase domain mutations, was reported in 10 patients[90]. The intracranial efficacy of larotrectinib has been demonstrated in several individuals with NTRK fusion-positive gliomas or brain metastases[405-407] .

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Nivolumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
35 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, hepatocellular carcinoma (HCC), classical Hodgkin lymphoma (cHL), and metastatic small cell lung cancer (SCLC). Furthermore, nivolumab is approved as both a single agent and in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[39,43] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. On the basis of prospective clinical data showing efficacy of nivolumab for patients with MSI-H CRC[8,408] , MSI-H status may predict sensitivity to nivolumab.

SUPPORTING DATA

A Phase 2 study of nivolumab, ipilimumab, and radiation therapy for patients with pretreated MSS metastatic colorectal cancer (CRC) reported an ORR of 10% (4/40, 1 CR) and a DCR of 25% (10/40)[409]. A patient with MMR-proficient CRC who harbored amplification of the PD-L1 and PD-L2 genes experienced clinical benefit from nivolumab[410]. The Phase 2 CheckMate 142 for patients with metastatic dMMR/MSI-H CRC receiving nivolumab combined with low-dose ipilimumab in the first-line setting achieved a 64% ORR (29/45, 4 CRs) and an 84% DCR; 15-month OS and PFS rates were 84% and 75%, respectively[411]. In the same study, patients with metastatic dMMR/MSI-H CRC who progressed on at least 1 previous line of treatment, nivolumab alone or combined with ipilimumab reported an ORR of 58% (69/119, 7 CRs) and an 81% DCR[408,412-413] . Biomarker analyses of CheckMate 142[411,414] , showed that responses were independent of PD-L1 expression levels, BRAF/KRAS mutation status, or history of Lynch syndrome across trial arms. Initial results from a Phase 1b/2 study evaluating nivolumab combined with capecitabine and irinotecan for previously treated metastatic CRC and pancreatic ductal adenocarcinoma cancer reported 1 PR out of 6 evaluable patients[415].

Panitumumab

Assay findings association

KRAS
wildtype

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.

GENE ASSOCIATION

Therapies targeting EGFR, including panitumumab, have been shown to have significant clinical activity in patients with CRC[58,416-417] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Guidelines v2.2019).

SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR in patients with KRAS wild-type CRC, both as first-line combination therapy with FOLFOX4[58] and as monotherapy for chemotherapy-refractory patients[416-417] . An open-label, randomized Phase 2 trial reported that in 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%)[418].

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

Pembrolizumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
35 Muts/Mb

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved for patients with microsatellite instability-high (MSI-H) or mismatch-repair-deficient (dMMR) solid tumors, MSI-H or dMMR colorectal cancer (CRC) that has progressed on specific therapies, or PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin lymphoma, cervical cancer, gastric cancer, esophageal cancer, or gastroesophageal junction (GEJ) carcinoma. It is also approved in various treatment settings for patients with melanoma, NSCLC, small cell lung cancer, HNSCC, urothelial carcinoma, hepatocellular carcinoma, or Merkel cell carcinoma. Combination treatments with pembrolizumab are approved for patients with NSCLC, renal cell carcinoma, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[39,43] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against MSI-H or mismatch repair-deficient (dMMR) solid tumors[9,419-423] , MSI-H status may predict sensitivity to pembrolizumab.

SUPPORTING DATA

A Phase 2 study of pembrolizumab for colorectal cancer (CRC) reported a significantly higher ORR (50% [14/28] vs. 0% [0/25]), DCR (89% [25/28] vs. 16% [4/25]), median PFS (not reached vs. 2.4 months, HR=0.135), and median OS (not reached vs. 6.0 months, HR=0.247) when comparing mismatch repair deficient (dMMR) and proficient (pMMR) samples[9,424]. The Phase 2 KEYNOTE-164 open-label study of pembrolizumab for the treatment of MSI-High/dMMR metastatic colorectal cancer with cohorts of ≥2 or ≥1 prior lines of therapy reported ORR of 33% and 33%, median PFS of 2.3 and 4.1 months, and median OSs of 31.4 months and not reached, respectively[425]. As part of the Phase 2 TAPUR trial, patients with high TMB (defined as ≥9 muts/MB) colorectal carcinoma treated with pembrolizumab achieved an ORR of 11.1% (3/27), a median PFS of 9.3 weeks, and a median OS of 51.9 weeks[426]. A Phase 2 study of pembrolizumab and azacitidine for patients with metastatic pMMR CRC reported an ORR of 3.3% (1/30), a median PFS of 1.9 months, and a median OS of 6.3 months[427]. A Phase 1b study of pembrolizumab combined with the ANG-1/2 inhibitor trebananib for solid tumors reported an ORR of 6.7% (1/25), a median PFS of 2.8 months, and a median OS of 9.0 months in patients with heavily pretreated MSI stable CRC[428]. Preliminary results from a Phase 2 study that combined adjuvant pembrolizumab with radiotherapy (RT) or ablation for pretreated metastatic CRC reported an ORR of 9% (1/11) for the RT arm and no responses in the ablation arm[429].

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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Atezolizumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
35 Muts/Mb

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and patients with either PD-L1-positive or -negative urothelial carcinoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, or PD-L1-positive triple-negative breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[39,43] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. On the basis of emerging clinical data showing efficacy of atezolizumab alone or in combination with antiangiogenic therapy for patients with MSI-H colorectal cancer[3] or endometrial cancer[4], MSI-H status may predict sensitivity to atezolizumab.

SUPPORTING DATA

For patients with chemotherapy-refractory metastatic colorectal cancer (CRC), the combination of atezolizumab with the MEK inhibitor cobimetinib did not significantly increase OS (8.9 vs. 8.5 months, HR=1.00) and achieved similar PFS (HR=1.25) and ORR outcomes (2.7% vs. 2.2%) compared with regorafenib in a Phase 3 trial, which included 54% KRAS-mutated and 92% MSS or MSI-Intermediate tumors; atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)[430]. A Phase 1b study also investigating cobimetinib in combination with atezolizumab reported a 8% ORR (7/84, all PRs) and median OS 9.8 months in patients with CRC; there was no association between BRAF or KRAS mutation status and response rate[431-432] . Out of 6 patients with CRC in a Phase 1 trial of atezolizumab, one patient with high PD-L1 expression on inflammatory cells experienced an objective response that was ongoing for more than 7 months[433].

Avelumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
35 Muts/Mb

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with Merkel cell carcinoma, or for urothelial carcinoma in various treatment settings. The combination of avelumab and axitinib is FDA approved for patients with renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[39,43] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. On the basis of emerging clinical data in patients with MSI-H colorectal cancer[3], endometrial cancer[4], or gastric/gastroesophageal junction cancer[5], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as avelumab.

SUPPORTING DATA

The JAVELIN Phase 1b study has demonstrated clinical benefit from single-agent avelumab in a variety of solid tumor types, including non-small cell lung carcinoma (NSCLC)[434], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[435], urothelial carcinoma[436], mesothelioma[437], ovarian carcinoma[438], and breast cancer[439], and from avelumab combined with axitinib in renal cell carcinoma[440]. Emerging clinical data show a positive trend toward the association of tumor cell PD-L1 expression and improved objective response rate, progression-free survival, or overall survival in NSCLC in the first-line setting and in ovarian and breast cancer[434,438-439] . Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[441-443] . The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS/BRAF wild-type metastatic CRC resulted in an ORR of 79.5% (6 CR and 25 PRs, n=39) and DCR of 92.3%[398].

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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Cemiplimab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
35 Muts/Mb

AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) that is not amenable to surgery or radiation therapy.

GENE ASSOCIATION

On the basis of clinical data[39,43] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. On the basis of prospective clinical data showing efficacy of anti-PD-1 therapies against various MSI-high (MSI-H) solid tumors[8-9,408,419-422] , MSI-H status may predict sensitivity to cemiplimab.

SUPPORTING DATA

Cemiplimab has been studied primarily in advanced CSCC, where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[444]. Clinical responses have also been reported in non-small cell lung cancer (40% ORR, 1 CR and 7 PRs) and basal cell carcinoma (1 PR)[445-446] .

Crizotinib

Assay findings association

NTRK1
TPM3-NTRK1 fusion

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are positive for ALK rearrangements or ROS1 rearrangements.

GENE ASSOCIATION

Alterations that activate NTRK1 may predict sensitivity to crizotinib. Clinical benefit with crizotinib treatment has been achieved in patients NTRK1-fusion-positive tumors including infantile fibrosarcoma[85-86,92] , lung adenocarcinoma[82,447] , and undifferentiated pleomorphic sarcoma[93].

SUPPORTING DATA

Out of 10 patients with MET-amplified colorectal cancer treated with crizotinib, 2 achieved stable disease[448]. Although a Phase 1b study evaluating crizotinib for the treatment of patients with ALK-positive malignancies reported a lower ORR in patients with various solid tumors relative to those with either lymphoma or inflammatory myofibroblastic tumors, a partial response was reported in a patient with colorectal cancer[449].

Durvalumab

Assay findings association

Microsatellite status
MSI-High

Tumor Mutational Burden
35 Muts/Mb

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with urothelial carcinoma, non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[39,43] , patients with CRC whose tumors harbor a tumor mutational burden (TMB) of 12 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1. On the basis of emerging clinical data in patients with MSI-H colorectal cancer[3], endometrial cancer[4], or gastric/gastroesophageal junction cancer[5], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as durvalumab.

SUPPORTING DATA

In a Phase 2 trial for patients with refractory metastatic colorectal cancer (CRC), the combination of durvalumab and tremelimumab elicited a higher DCR than best supportive care (22.6% vs. 6.6%) but did not significantly increase median PFS (1.8 vs. 1.9 months) or OS (6.6 vs. 4.1 months, HR=0.72, p=0.07) in the overall population[450]. For patients with MSS tumors (OS HR=0.66), TMB greater than 28 muts/Mb was associated with greatest OS benefit (HR=0.34, p=0.07) from durvalumab/tremelimumab[450].

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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Niraparib

Assay findings association

ATM
R3047*

PALB2
M296fs*1

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved for the maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Niraparib is also approved to treat advanced ovarian, Fallopian tube, or primary peritoneal cancer with homologous recombination deficiency (HRD)-positive status after 3 or more prior lines of chemotherapy.

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 breast cancer[451], gastric cancer[123], bladder cancer[452], and papillary renal cell carcinoma[453]. On the basis of cases of clinical benefit in pancreatic, ovarian and prostate cancer[122,147,454] and strong preclinical data[149-150] , loss or inactivation of PALB2 may confer sensitivity to PARP inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of colorectal cancer are limited (PubMed, Feb 2020). 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)[455]. 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[456]. 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)[457].

Olaparib

Assay findings association

ATM
R3047*

PALB2
M296fs*1

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, with or without deleterious or suspected deleterious somatic or germline BRCA (gBRCA) mutations, as well as deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast 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 breast cancer[451], gastric cancer[123], bladder cancer[452], and papillary renal cell carcinoma[453]. On the basis of cases of clinical benefit in pancreatic, ovarian and prostate cancer[122,147,454] and strong preclinical data[149-150] , loss or inactivation of PALB2 may confer sensitivity to PARP inhibitors.

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[458]. 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[459-460] . Olaparib treatment has also demonstrated clinical activity for patients with breast, prostate, or pancreatic cancer and BRCA1/2 mutations[459-463] .

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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Rucaparib

Assay findings association

ATM
R3047*

PALB2
M296fs*1

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations who have been previously treated with two or more chemotherapies. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

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 breast cancer[451], gastric cancer[123], bladder cancer[452], and papillary renal cell carcinoma[453]. On the basis of cases of clinical benefit in pancreatic, ovarian and prostate cancer[122,147,454] and strong preclinical data[149-150] , loss or inactivation of PALB2 may confer sensitivity to PARP inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of colorectal cancer are limited (PubMed, Feb 2020). 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[464]. 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[362]. 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[465]. 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[466]. 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[467]. 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[468]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[469]. 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[470].

Talazoparib

Assay findings association

ATM
R3047*

PALB2
M296fs*1

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.

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 breast cancer[451], gastric cancer[123], bladder cancer[452], and papillary renal cell carcinoma[453]. On the basis of clinical benefit in breast, bladder, pancreatic, ovarian, and prostate cancer[122,147,451-452,454,471] , PALB2 inactivation may predict sensitivity to PARP inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of talazoparib for the treatment of colorectal cancers are limited (PubMed, Feb 2020). 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[472-473] . 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[451]. 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[471,474-476] .

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.

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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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.

BIOMARKER
Microsatellite status

RESULT
MSI-High

RATIONALE
High microsatellite instability (MSI) and mutational burden may predict response to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors.

NCT02912559

PHASE 3

Combination Chemotherapy With or Without Atezolizumab in Treating Patients With Stage III Colon Cancer and Deficient DNA Mismatch Repair or Microsatellite Instability

TARGETS
PD-L1

LOCATIONS: California

NCT02997228

PHASE 3

Combination Chemotherapy, Bevacizumab, and/or Atezolizumab in Treating Patients With Microsatellite Instability-High Metastatic Colorectal Cancer

TARGETS
VEGFA, PD-L1

LOCATIONS: California, Nevada

NCT02693535

PHASE 2

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

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: California, Oregon, Utah, Arizona, Washington, North Dakota, South Dakota, Nebraska

NCT03170960

PHASE 1/2

Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-L1, MET, RET, ROS1, VEGFRs

LOCATIONS: California, Nevada, Oregon, Utah, Arizona

NCT03010176

PHASE 1

Study of MK-1454 Alone or in Combination With Pembrolizumab in Participants With Advanced/Metastatic Solid Tumors or Lymphomas (MK-1454-001)

TARGETS
STING, PD-1

LOCATIONS: California, Utah, Texas, Alabama, New York, London (United Kingdom), Paris (France), Villejuif (France), Seoul (Korea, Republic of)

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Foundation Medicine, Inc. | 1.888.988.3639

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CLINICAL TRIALS

NCT03289962

PHASE 1

A Study of RO7198457 as a Single Agent and in Combination With Atezolizumab in Participants With Locally Advanced or Metastatic Tumors

TARGETS
PD-L1

LOCATIONS: California, Nevada, Oregon, Arizona, Washington, Colorado, Oklahoma, Tennessee, Toronto (Canada)

NCT03260322

PHASE 1

A Multiple-dose Study of ASP8374, an Immune Checkpoint Inhibitor, as a Single Agent and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors

TARGETS
TIGIT, PD-1

LOCATIONS: California, Utah, Arizona, Edmonton (Canada), Texas, Kansas, Iowa

NCT02715284

PHASE 1

A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Patients With Advanced Solid Tumors

TARGETS
PD-1

LOCATIONS: California, Oregon, Arizona

NCT03517488

PHASE 1

A Study of XmAb®20717 in Subjects With Selected Advanced Solid Tumors

TARGETS
CTLA-4, PD-1

LOCATIONS: California, Oregon, Utah, Washington, Kansas, Texas, Illinois, Michigan

NCT02983045

PHASE 1/2

A Dose Escalation and Cohort Expansion Study of CD122-Biased Cytokine (NKTR-214) in Combination With Anti-PD-1 Antibody (Nivolumab) in Patients With Select Advanced or Metastatic Solid Tumors

TARGETS
PD-1, CD122, CTLA-4

LOCATIONS: California, Oregon, Washington, Colorado, Kansas, Texas, Missouri, Illinois

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

BIOMARKER

Tumor Mutational Burden

RESULT

35 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 or anti-PD-L1 immune checkpoint inhibitors.

NCT02091141

PHASE 2

A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf/Cotellic, and Erivedge Treatment Targeted Against Certain Mutations in Cancer Patients

TARGETS
ERBB3, ERBB2, EGFR, BRAF, MEK, SMO, ALK, RET, PD-L1

LOCATIONS: California, Arizona, Washington, New Mexico

NCT02693535

PHASE 2

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

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: California, Oregon, Utah, Arizona, Washington, North Dakota, South Dakota, Nebraska

NCT03170960

PHASE 1/2

Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-L1, MET, RET, ROS1, VEGFRs

LOCATIONS: California, Nevada, Oregon, Utah, Arizona

NCT03010176

PHASE 1

Study of MK-1454 Alone or in Combination With Pembrolizumab in Participants With Advanced/Metastatic Solid Tumors or Lymphomas (MK-1454-001)

TARGETS
STING, PD-1

LOCATIONS: California, Utah, Texas, Alabama, New York, London (United Kingdom), Paris (France), Villejuif (France), Seoul (Korea, Republic of)

NCT03289962

PHASE 1

A Study of RO7198457 as a Single Agent and in Combination With Atezolizumab in Participants With Locally Advanced or Metastatic Tumors

TARGETS
PD-L1

LOCATIONS: California, Nevada, Oregon, Arizona, Washington, Colorado, Oklahoma, Tennessee, Toronto (Canada)

NCT03260322

PHASE 1

A Multiple-dose Study of ASP8374, an Immune Checkpoint Inhibitor, as a Single Agent and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors

TARGETS
TIGIT, PD-1

LOCATIONS: California, Utah, Arizona, Edmonton (Canada), Texas, Kansas, Iowa

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CLINICAL TRIALS

NCT02715284

PHASE 1

A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Patients With Advanced Solid Tumors

TARGETS
PD-1

LOCATIONS: California, Oregon, Arizona

NCT02983045

PHASE 1/2

A Dose Escalation and Cohort Expansion Study of CD122-Biased Cytokine (NKTR-214) in Combination With Anti-PD-1 Antibody (Nivolumab) in Patients With Select Advanced or Metastatic Solid Tumors

TARGETS
PD-1, CD122, CTLA-4

LOCATIONS: California, Oregon, Washington, Colorado, Kansas, Texas, Missouri, Illinois

NCT03454451

PHASE 1

CPI-006 Alone and in Combination With CPI-444 and With Pembrolizumab for Patients With Advanced Cancers

TARGETS
PD-1, ADORA2A, CD73

LOCATIONS: California, Nevada, Arizona, Oklahoma, Texas, Wisconsin, Illinois, Tennessee, Ohio

NCT03071757

PHASE 1

A Study of the Safety, Tolerability and Pharmacokinetics of ABBV-368 as a Single Agent and Combination in Subjects With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-1, OX40

LOCATIONS: California, Texas, South Carolina, North Carolina, Virginia, Connecticut, Rio Piedras (Puerto Rico)

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GENE
ATM

ALTERATION
R3047*

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

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: California, Utah, Washington, Arizona, Chihuahua (Mexico), Nebraska, South Dakota, Oklahoma

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: California, Utah, Washington, Texas, Kentucky, Georgia, Ohio, Florida, Virginia

NCT02693535

PHASE 2

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

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: California, Oregon, Utah, Arizona, Washington, North Dakota, South Dakota, Nebraska

NCT03330405

PHASE 2

Javelin Parp Medley: Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors

TARGETS
PD-L1, PARP

LOCATIONS: California, Edmonton (Canada), Arkansas, Minnesota, Texas

NCT03682289

PHASE 2

Phase II Trial of AZD6738 Alone and in Combination With Olaparib

TARGETS
ATR, PARP

LOCATIONS: California

NCT03318445

PHASE 1

Rucaparib and Irinotecan in Cancers With Mutations in DNA Repair

TARGETS
PARP, TOP1

LOCATIONS: California

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CLINICAL TRIALS

NCT02595931

PHASE 1

ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
ATR

LOCATIONS: California, Tennessee, Pennsylvania, Florida, North Carolina, Connecticut, Massachusetts

NCT03329001

PHASE 1

Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Compared to Niraparib Capsule

TARGETS
PARP

LOCATIONS: California, Colorado, Oklahoma, Texas, Tennessee, Michigan, Ohio

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT03830918

PHASE 1/2

Niraparib and Temozolomide in Treating Patients With Extensive-Stage Small Cell Lung Cancer With a Complete or Partial Response to Platinum-Based First-Line Chemotherapy

TARGETS
PARP

LOCATIONS: California

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GENE
CTNNB1

ALTERATION
W383R

RATIONALE
Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive 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. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

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

NCT02890069

PHASE 1

A Study of PDR001 in Combination With LCL161, Everolimus or Panobinostat

TARGETS
mTOR, PD-1, CXCR2, HDAC, MDM2, IAPs

LOCATIONS: California, Utah, Washington, Texas, Michigan, Maryland, Massachusetts, Manchester (United Kingdom), Sutton (United Kingdom), Amsterdam (Netherlands)

NCT02719691

PHASE 1

Phase I Study of MLN0128 and MLN8237 in Patients With Advanced Solid Tumors and Metastatic Triple-negative Breast Cancer

TARGETS
Aurora kinase A, mTORC1, mTORC2

LOCATIONS: Colorado

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

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

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CLINICAL TRIALS

NCT03154294

PHASE 1

Evaluation of the Safety and Tolerability of TAK-228 With TAK-117 and Paclitaxel in Advanced Solid Tumors

TARGETS
PI3K-alpha, mTORC1, mTORC2

LOCATIONS: South Dakota

NCT03017833

PHASE 1

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

TARGETS
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

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

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GENE
NTRK1

RATIONALE
NTRK1 activating fusions may predict sensitivity to TRK inhibitors or crizotinib.

ALTERATION
TPM3-NTRK1 fusion

NCT02568267

PHASE 2

Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: California, Nevada, Oregon, Utah, Arizona

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

LOCATIONS: California, Oregon

NCT03215511

PHASE 1/2

Phase 1/2 Study of LOXO-195 in Patients With Previously Treated NTRK Fusions or Non-fusion NTRK Cancers

TARGETS
TRKA, TRKB, TRKC

LOCATIONS: California, Oregon, Utah, Washington, Colorado, Texas, Tennessee

NCT03093116

PHASE 1/2

A Study of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: California, Washington, Colorado, Edmonton (Canada), Texas

NCT02637687

PHASE 1/2

Oral TRK Inhibitor LOXO-101 (Larotrectinib) for Treatment of Advanced Pediatric Solid or Primary Central Nervous System Tumors

TARGETS
TRKA, TRKB, TRKC

LOCATIONS: Toronto (Canada), Montreal (Canada), Crumlin (Ireland), Yokohama (Japan), Stockholm (Sweden), Sutton (United Kingdom), Osaka (Japan), Copenhagen (Denmark), PARIS cedex 5 (France), Villejuif Cedex (France)

NCT02576431

PHASE 2

Study of LOXO-101 in Subjects With NTRK Fusion Positive Solid Tumors (NAVIGATE)

TARGETS
TRKA, TRKB, TRKC

LOCATIONS: Dublin (Ireland), Kashiwa (Japan), Copenhagen (Denmark), Porto (Portugal), Seoul (Korea, Republic of), Berlin (Germany), Bordeaux Cedex (France), Madrid (Spain), Singapore (Singapore)

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GENE
PALB2

ALTERATION
M296fs*1

RATIONALE
Tumors with PALB2 mutation or loss may be sensitive to PARP inhibitors.

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: California, Utah, Washington, Arizona, Chihuahua (Mexico), Nebraska, South Dakota, Oklahoma

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: California, Utah, Washington, Texas, Kentucky, Georgia, Ohio, Florida, Virginia

NCT02693535

PHASE 2

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

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: California, Oregon, Utah, Arizona, Washington, North Dakota, South Dakota, Nebraska

NCT03682289

PHASE 2

Phase II Trial of AZD6738 Alone and in Combination With Olaparib

TARGETS
ATR, PARP

LOCATIONS: California

NCT03318445

PHASE 1

Rucaparib and Irinotecan in Cancers With Mutations in DNA Repair

TARGETS
PARP, TOP1

LOCATIONS: California

NCT03329001

PHASE 1

Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Compared to Niraparib Capsule

TARGETS
PARP

LOCATIONS: California, Colorado, Oklahoma, Texas, Tennessee, Michigan, Ohio

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CLINICAL TRIALS

NCT04171700

PHASE 2

A Study to Evaluate Rucaparib in Patients With Solid Tumors and With Deleterious Mutations in HRR Genes

TARGETS
PARP

LOCATIONS: California, Washington, Iowa, Tennessee, Florida, Pennsylvania, New York

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT03830918

PHASE 1/2

Niraparib and Temozolomide in Treating Patients With Extensive-Stage Small Cell Lung Cancer With a Complete or Partial Response to Platinum-Based First-Line Chemotherapy

TARGETS
PARP

LOCATIONS: California

NCT02997176

PHASE 1

An Open-Label Pharmacokinetics and Safety Study of Talazoparib (MDV3800)

TARGETS
PARP

LOCATIONS: California, Texas, Georgia

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GENE
RNF43

ALTERATION
G659fs*41

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

NCT01351103

PHASE 1

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

TARGETS
PORCN, PD-1

LOCATIONS: California, Texas, Michigan, Maryland, Massachusetts, Rotterdam (Netherlands), Utrecht (Netherlands), Madrid (Spain), Barcelona (Spain)

NCT03447470

PHASE 1

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

TARGETS
PORCN

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

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GENE
SUFU

ALTERATION
A25fs*23

RATIONALE
Inactivation of SUFU may lead to increased GLI transcriptional activity, which has been shown to be dependent on the BET bromodomain protein BRD4. Therefore, BET inhibitors may be appropriate in the context of a SUFU mutation.

NCT02419417

PHASE 1/2

Study of BMS-986158 in Subjects With Select Advanced Solid Tumors

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: California, Oregon, Colorado, South Carolina, Ottawa (Canada), Pennsylvania, Massachusetts, Villejuif (France), Pamplona (Spain), Madrid (Spain)

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

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

NCT03205176

PHASE 1

AZD5153 in Patients With Relapsed or Refractory Solid Tumors, Including Lymphomas

TARGETS
BRD4, PARP

LOCATIONS: Oklahoma, Tennessee, Toronto (Canada), Florida

NCT02516553

PHASE 1

BI 894999 First in Human Dose Finding Study in Advanced Malignancies

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Massachusetts, Gent (Belgium), Bruxelles (Belgium), Villejuif (France), Tübingen (Germany)

NCT03220347

PHASE 1

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

TARGETS
BRD2, BRD3, BRD4, BRDT

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

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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.

ALK E160fs*26	***AXIN1*** R477H	***BRAF*** P403fs*8	***CASP8*** P349H and V371A
CBL M487V	***CD22*** A656V	***CD70*** T111M	***EED*** C330Y
EPHA3 T802M	***EPHB1*** P419T	***ERBB3*** S413fs*38	***ESR1*** R243H
FGF10 N159fs*10	***IRS2*** N28del	***LTK*** D681fs*76	***MEN1*** A385T and W346C
MLL2 P530A	***NKX2-1*** G89D	***PIK3C2G*** V65fs*16	***POLE*** R1878C
PPP2R2A R389H	***PRKCI*** T276fs*7	***SETD2*** G1014C	***SMARCA4*** M949V
SMO G630*	***ZNF217*** L731V		

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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) and tumor mutational burden (TMB) 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 the targeted therapies listed in Table 1 in accordance with the 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. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

The test is also used for detection of genomic loss of heterozygosity (LOH) from FFPE ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the RUBRACA product label.

The F1CDx assay will be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E and V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib), in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)

The median exon coverage for this sample is 949x

Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

TEST PRINCIPLE

FoundationOne®CDx (F1CDx) is performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The assay employs 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 (refer to Table 2 and Table 3 for complete list of genes included in F1CDx). In total, the assay detects alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid capture–selected libraries are sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data is then processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous gene deletions), and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and positive homologous recombination deficiency (HRD) status (tBRCA-positive and/or LOH high) are reported.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/f1cdx

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.
4. Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*.
5. Clinical performance of Tagrisso® (osimertinib) in patients with an *EGFR* exon 20 T790M mutation detected with an allele fraction <5% is ongoing and has not been established.
6. Concordance with other validated methods for CNA (with the exception of *ERBB2*) and gene rearrangement (with the exception of *ALK*) detection has not been demonstrated and will be provided in the post-market setting. Confirmatory testing using a clinically validated assay should be performed for all CNAs and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use, but used for clinical decision making.
7. The MSI-H/MSS designation by FMI FoundationOne®CDx (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. Refer https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf for additional details on methodology. 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. Patients with microsatellite status of "Cannot Be Determined" should be retested with an orthogonal (alternative) method. The clinical validity of the qualitative MSI designation has not been established.
8. TMB by F1CDx is defined based by counting the total number of all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit. TMB is a function of the characteristics of a patient's specimen and testing parameters; therefore, TMB may differ among specimens (e.g., primary vs. metastatic, tumor content) and targeted panels. 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 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 not been established.
9. 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.
10. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.
11. Alterations in polyT homopolymer runs may not be reliably detected in BRCA1/2.
12. Certain large rearrangements in BRCA1/2 including large scale genomic deletions (affecting at least one whole exon), insertions or other deleterious genomic rearrangements

including inversions or transversion events, may not be detected in an estimated 5% of ovarian cancer patients with BRCA1/2 mutations by F1CDx.

13. Certain potentially deleterious missense or small in-frame deletions in BRCA1/2 may not be reported under the "CDx associated findings" but may be reported in the "Other alterations and biomarkers identified" section in the patient report.
14. Alterations at allele frequencies below the established limit of detection may not be detected consistently.
15. Detection of LOH has been verified only for ovarian cancer patients.
16. Performance of the LOH classification has not been established for samples below 35% tumor content and with LOH scores near the cutoff of 16.
17. 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.

PDF Service Version 2.9.0

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)

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.

PROFESSIONAL SERVICES FINDINGS

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.

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.

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. 2020. All rights reserved. To view the most recent and complete version of the guideline, 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

Foundation Medicine makes no promises or guarantees that a particular drug will be effective in the treatment of disease of 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 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 with the 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.

LOSS OF HETEROZYGOSITY SCORE

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. 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.

MICROSATELLITE STATUS

For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.

TUMOR MUTATIONAL BURDEN

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations in sequenced genes on the FoundationOne CDx test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne CDx samples and is reported in Professional Services as the number of mutations per megabase (Muts/Mb) rounded to the nearest integer. Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

Genomic Findings with Evidence of Clinical Significance

Genomic findings listed at Level 2 are associated with clinical significance. Clinical significance may be indicated by evidence of therapeutic sensitivity or resistance and/or diagnostic, prognostic or other clinically relevant implications. Included in this category will be findings associated with clinical validity as supported by professional guidelines and/or peer-reviewed publications.

Genomic Findings with Potential Clinical Significance

Genomic findings listed at Level 3 are cancer-related mutations and biomarkers with potential clinical significance. These include findings in genes known to be associated with cancer and are supported by evidence from publicly available databases, and/or peer-reviewed publications.

A Fluid Approach to Reporting Levels

As additional information becomes available, as recognized by the clinical community (professional guidelines and/or peer-reviewed publications), findings may move between Levels 2 and 3 in accordance with the above descriptions.

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

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APPENDIX References Associated with Professional Services Content

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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Electronically signed by Richard Huang, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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