FOUNDATIONONE®CDx

PATIENT
Ho, Huan-Chen

TUMOR TYPE
Colon adenocarcinoma (CRC)
COUNTRY CODE
TW

REPORT DATE
29 Jun 2022
ORDERED TEST #
ORD-1395291-01

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

PATIENT
DISEASE Colon adenocarcinoma (CRC)
NAME Ho, Huan-Chen
DATE OF BIRTH 28 October 1961
SEX Male
MEDICAL RECORD # 34518279

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

SPECIMEN
SPECIMEN SITE Colon
SPECIMEN ID S107-60194 F (PF22072)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 16 January 2018
SPECIMEN RECEIVED 21 June 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings

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

ERBB2 amplification - equivocal†
KRAS wildtype
NRAS wildtype
APC Q1447*
PIK3CA M1043V
FAM123B E637*
TP53 V147fs*2

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

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Fam-trastuzumab deruxtecan** (p. 11), **Trastuzumab + Pertuzumab** (p. 13)
- Targeted therapies with **potential resistance** based on this patient's genomic findings: **Cetuximab** (p. 9), **Panitumumab** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 14)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ERBB2 **-** amplification - equivocal	*Cetuximab* ⊗	Fam-trastuzumab deruxtecan 2A
	Panitumumab ⊗	Trastuzumab + Pertuzumab 2A
		Ado-trastuzumab emtansine
		Margetuximab
10 Trials *see p. 15*		Trastuzumab
		Trastuzumab + Tucatinib
KRAS **-** wildtype	*Cetuximab* ⊗	none
0 Trials	*Panitumumab* ⊗	
NRAS **-** wildtype	*Cetuximab* ⊗	none
0 Trials	*Panitumumab* ⊗	
APC **-** Q1447*	none	none
4 Trials *see p. 14*		
PIK3CA **-** M1043V	none	none
10 Trials *see p. 17*		

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

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5]. For patients with chemotherapy-refractory microsatellite-stable (MSS) metastatic colorectal cancer (CRC), a Phase 3 trial reported no OS advantage from the combination of the PD-L1 inhibitor atezolizumab plus cobimetinib relative to regorafenib (8.9 vs. 8.5 months, HR=1.00); atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)[6]. For patients with MSS CRC, a Phase 2 study combining ipilimumab and nivolumab reported an overall DCR of 25% (10/40)[7]. Two Phase 1 studies for patients with MSS CRC treated with regorafenib and nivolumab reported PFSs of 7.9 months[8] and 5.7 months[9], and a patient with MSS CRC refractory to chemotherapy treated with the PD-1 inhibitor sintilimab and regorafenib reported a CR[10].

— Nontargeted Approaches —

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[20]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[20,30-31]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19,32-33]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[19-20,31,33].

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

BIOMARKER

Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[34-36], anti-PD-1 therapies[34-37], and combination nivolumab and ipilimumab[38-43]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[34-37,44-48]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[44]; similar findings were observed in the KEYNOTE 028 and 012 trials[37]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[48]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[49]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[47]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[50] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[35]. In CRC specifically, a retrospective analysis of immune checkpoint inhibitor efficacy reported significantly improved OS for patients with tumors harboring TMB ≥9.8 Muts/MB compared with those with tumors with TMB <9.8 Muts/Mb (~ equivalency <12 Muts/Mb as measured by this assay)[34]. Another retrospective study reported that a TMB ≥12 Muts/Mb cutoff identifies >99% of MSI-High CRC cases but only 3% of MSS cases, indicating the utility of this cutoff for identification of patients with CRC likely to benefit from treatment with immune checkpoint inhibitors[51].

FREQUENCY & PROGNOSIS

Elevated tumor mutational burden (TMB) has been reported in 8-25% of colorectal cancer (CRC) samples[21,52-53]. Multiple studies have reported that up to 90% of hypermutated CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)[21,52]. Increased TMB is significantly associated with MSI-H and MMR-D, with studies reporting that 100% of MSI-H CRCs harbor elevated TMB and conversely that 100% of tumors with low TMB harbor intact MMR[52]. A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which leads to an "ultramutated" phenotype with especially high TMB[21,52]. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB[21,52], whereas TMB-low tumors more frequently harbor mutations in TP53 and APC[21]. The prognostic value of tumor mutational burden (TMB) in colorectal cancer (CRC) is context- and therapy-dependent. A study of tissue TMB (tTMB) in 145 CRC samples showed longer OS in TMB-high samples compared with TMB-low ones[54]. Similarly, for patients with metastatic CRC treated with first-line chemotherapy combined with bevacizumab or cetuximab, high tissue TMB (tTMB-H) was associated with longer OS[55]. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival[56]. However, for patients with EGFR/BRAF-inhibitor-treated, BRAF-mutated microsatellite stable (MSS) metastatic CRC, intermediate tTMB was associated with significantly poorer PFS and OS compared with TMB-low status; patients with primary resistance to EGFR/BRAF blockage had higher TMB than those sensitive to these therapies[57]. In a study for 61 patients with metastatic, MSS CRC treated with best standard of care, plasma TMB scores ≥28 Muts/Mb (approximately 14 Muts/Mb as measured by this assay) were associated with reduced OS compared with plasma TMB scores <28 Muts/Mb (3.0 vs. 5.3 months, HR=0.76, p=0.007), whereas tTMB was not found to be prognostic in this population[58].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[59-60] and cigarette smoke in lung cancer[61-62], treatment with temozolomide-based chemotherapy in glioma[63-64], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[21,65-68], and microsatellite instability (MSI)[21,65,68]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[34,44,51].

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

GENE
ERBB2

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[69-74], pertuzumab in combination with trastuzumab[71,75-77], and zanidatamab (ZW25)[78], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[79] and fam-trastuzumab deruxtecan[80], HER2 kinase inhibitors such as tucatinib[81-84], and dual EGFR/HER2 kinase inhibitors such as lapatinib[85-93], afatinib[74,94-103], neratinib[104-107], dacomitinib[108], and pyrotinib[109-110]. HER2-targeted therapies have demonstrated clinical benefit for patients with HER2-positive metastatic colorectal cancer (CRC) that is RAS/BRAF-wildtype. In Phase 2 studies, the combination of trastuzumab plus pertuzumab achieved an ORR of 32% (18/57, 1 CR)[77], the combination of trastuzumab plus lapatinib achieved an overall response rate of 30% (8/27, 1 CR)[111], and trastuzumab deruxtecan elicited an ORR of 45% (24/53, 1 CR)[112]. Other HER2 targeted therapies have been evaluated for patients with HER2-positive metastatic CRC including tucatinib plus trastuzumab (ORR of 55%, 12/22)[113], pyrotinib plus trastuzumab (ORR of 27%, 3/11)[114], and HER2 targeted antibody-drug conjugate A166[115].

— Potential Resistance —

Tyrosine kinase inhibitors such as afatinib and lapatinib have yielded limited clinical efficacy as monotherapies in CRC, suggesting antibody therapeutics or combination therapies may be more beneficial in this tumor type[116-119]. In a Phase 2 trial, the combination of trastuzumab and lapatinib demonstrated significant clinical activity in patients with HER2-positive, KRAS exon 2 wild-type colorectal cancer, achieving an ORR of 30% (8/27), including 1 CR[111]. Preclinical and clinical data suggest that ERBB2 amplification in colorectal cancer is associated with lack of response to the EGFR antibodies cetuximab and panitumumab[120-121], and a combination of therapies targeting both EGFR and ERBB2 was effective in treating tumors with ERBB2 amplification in a preclinical setting[120,122]. ERBB2 amplification has been associated with lack of response to EGFR inhibition in clinical and preclinical studies of KRAS/NRAS wild-type colorectal cancer (CRC) and was observed in patients after development of resistance to cetuximab or panitumumab (NCCN Colon Cancer Guidelines, v2.2021)[120,122-131]; although clinical responses to these agents have been reported for patients with ERBB2-amplified CRC, reported response rates have been much lower than those for patients with CRC lacking ERBB2 amplification or overexpression[125,131-133].

FREQUENCY & PROGNOSIS

ERBB2 mutation or amplification was observed in 4% and 2-6% of colorectal adenocarcinoma cases, respectively[21,134-136]. ERBB2 amplification has been associated with protein overexpression in colorectal cancer[136-137]. For patients with colorectal cancer, multiple studies have shown that ERBB2 overexpression does not correlate with survival[136-138] and is not considered prognostic (NCCN Colon Cancer Guidelines, v3.2021); however, studies have shown an association of ERBB2 amplification with reduced response and/or shorter survival for patients treated with anti-EGFR antibodies[125,133].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation[139].

GENE
KRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[140-143] or panitumumab[144-146] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v3.2021).

FREQUENCY & PROGNOSIS

Approximately 50-65% of colorectal cancers (CRCs) have been reported to lack KRAS mutations[147-155]. Numerous studies have reported that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC[149-152,156-157].

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[158-159]. No alterations in KRAS were identified in this case.

GENE
NRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[140-143] or panitumumab[144-146] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v3.2021).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[21,155,160-165]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[155] and longer survival[165-166] 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[158]. No alterations in NRAS were identified in this case.

GENE
APC

ALTERATION
Q1447*

TRANSCRIPT ID
NM_000038

CODING SEQUENCE EFFECT
4339C>T

VARIANT ALLELE FREQUENCY (% VAF)
35.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs[167], and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP[168-169]. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days[170]; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386[171-172].

FREQUENCY & PROGNOSIS

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset[21]. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples[173]. The prognostic significance of APC mutations in sporadic CRC remains unclear[174]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[175].

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[176]. Alterations such as seen here may disrupt APC function or expression[177-181].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[182-184]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[185], and in the appropriate clinical context germline testing of APC is recommended.

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

GENE
PIK3CA

ALTERATION
M1043V

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
3127A>G

VARIANT ALLELE FREQUENCY (% VAF)
6.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[186-193], AKT[194-195], or mTOR[196-203]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[193]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[192]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[190-191]. Emerging evidence suggests that the glutaminase inhibitor telaglenastat has clinical activity in PIK3CA-mutated colorectal cancer (CRC). A Phase 1 trial of telaglenastat and capecitabine for patients with CRC who progressed on fluoropyrimidine chemotherapy observed numerically increased median PFS for patients with PIK3CA mutation compared with patients with wildtype PIK3CA status (24.8 vs. 16 weeks, n=7 vs. n=4), including SD >30 weeks for 3 patients with PIK3CA mutation[204].

— Potential Resistance —

Multiple clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies to treat CRC, even for tumors that harbor alterations in PIK3CA or PTEN; data are more limited for alterations in other genes in this pathway[200,205-206].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in up to 19% of colorectal cancers (CRCs)[21,207]. A meta-analysis of 864 patients with colorectal cancer treated with cetuximab- or panitumumab-based therapy showed that PIK3CA mutations, particularly in exon 20 (H1047R), are significantly associated with worse response[208] and shorter progression-free and overall survival[163]. A study of 354 patients with metastatic colorectal cancer observed no difference in overall survival between patients with PIK3CA mutations versus those without (21.7 months vs. 22.4 months, respectively); however, the study did not include treatment information for the patients[209].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[210-211]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[212-233].

GENE
FAM123B

ALTERATION
E637*

TRANSCRIPT ID
NM_152424

CODING SEQUENCE EFFECT
1909G>T

VARIANT ALLELE FREQUENCY (% VAF)
65.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

Somatic mutation of FAM123B is rare in most cancers (COSMIC, 2022)[234], but is observed at rates ranging from 5-30% in Wilms tumor[235-237]. 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[238]. Germline mutation or deletion of FAM123B causes osteopathia striata with cranial sclerosis[239-240].

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

GENE
TP53

ALTERATION
V147fs*2

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
439_440insG

VARIANT ALLELE FREQUENCY (% VAF)
49.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[241-244], or p53 gene therapy and immunotherapeutics such as SGT-53[245-249] and ALT-801[250]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[251]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[252]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[253]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[254]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[255]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[256]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[257]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[249]. 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[258-259]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[260-261]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 75% of colorectal cancer cases[21,262-267]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[268]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[269].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[270]. Alterations such as seen here may disrupt TP53 function or expression[271-275].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[276-278], including sarcomas[279-280]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[281] to 1:20,000[280]. 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[282]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[283-288]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[283-284]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[289]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[287,290-291]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

Cetuximab

Resistance of variant(s) to associated therapy is likely

Assay findings association

ERBB2
amplification - equivocal

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). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including cetuximab, have been shown to have significant clinical activity for patients with CRC[140-143,292-293] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2021). Generally mutually exclusive with NRAS or KRAS alterations, ERBB2 amplification may reduce response to cetuximab and panitumumab for patients with colorectal cancer (CRC) and is recommended for molecular testing as part of the diagnostic workup by the NCCN, particularly for patients lacking RAS mutations (NCCN Colon Cancer Guidelines, v2.2021). ERBB2 amplification has been associated with significantly inferior PFS[124-125,131,294] or OS[122,124-125] , as well as lower ORRs[120,126,131,133] , for cetuximab- or panitumumab-treated patients with NRAS/KRAS-wild-type CRC with co-occurring ERBB2 amplification versus those without; a small number of retrospective studies have reported similar but nonsignificant trends for shorter PFS[122,133] and OS[124] or reduced ORR[125] for patients with ERBB2-amplified versus non-amplified CRC. ERBB2 amplification has been reported in patients with NRAS- and KRAS-wild-type CRC who progressed on cetuximab- or panitumumab-based regimens[123-124,127-129] to these agents. Taken collectively, it is therefore unlikely that cetuximab or panitumumab would be beneficial for patients with ERBB2 amplification, as in this case.

SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wildtype CRC, both in combination with FOLFIRI, FOLFOX4, or irinotecan[140-141,292-293,295] and as monotherapy for chemotherapy-refractory patients[143,296] . A prospective study of cetuximab for patients with KRAS/NRAS/BRAF mutation-negative metastatic CRC resulted in limited efficacy, with 11% (2/19) of participants experiencing PRs and 58% (11/19) experiencing SDs[297]. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wildtype metastatic CRC resulted in an ORR of 81% (4 CR and 27 PRs, n=37) and a DCR of 89%[298]. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)[299]. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)[300].

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

Panitumumab

Resistance of variant(s) to associated therapy is likely

Assay findings association

ERBB2
amplification - equivocal

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. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including panitumumab, have been shown to have significant clinical activity for patients with CRC[144,299,301] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2021). Generally mutually exclusive with NRAS or KRAS alterations, ERBB2 amplification may reduce response to cetuximab and panitumumab for patients with colorectal cancer (CRC) and is recommended for molecular testing as part of the diagnostic workup by the NCCN, particularly for patients lacking RAS mutations (NCCN Colon Cancer Guidelines, v2.2021). ERBB2 amplification has been associated with significantly inferior PFS[124-125,131,294] or OS[122,124-125] , as well as lower ORRs[120,126,131,133] , for cetuximab- or panitumumab-treated patients with NRAS/KRAS-wild-type CRC with co-occurring ERBB2 amplification versus those without; a small number of retrospective studies have reported similar but nonsignificant trends for shorter PFS[122,133] and OS[124] or reduced ORR[125] for patients with ERBB2-amplified versus non-amplified CRC. ERBB2 amplification has been reported in patients with NRAS- and KRAS-wild-type CRC who progressed on cetuximab- or panitumumab-based regimens[123-124,127-129] to these agents. Taken collectively, it is therefore unlikely that cetuximab or panitumumab would be beneficial for patients with ERBB2 amplification, as in this case.

SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS wildtype CRC, both in combination with FOLFOX4, FOLFIRI, irinotecan, or best supportive care[144,302-304] and as monotherapy for chemotherapy-refractory patients[265,299,301] . A Phase 2 trial reported that for patients with unresectable RAS-wildtype colorectal adenocarcinoma treated with panitumumab plus FOLFOX4, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS, 59% vs. 49%)[305]. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)[299]. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)[300].

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

Ado-trastuzumab emtansine

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy as well as patients with HER2+ early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1[79,306-321] .

SUPPORTING DATA

The Phase 2 NCI-MATCH subprotocol of T-DM1 in ERBB2-amplified (ERBB2+) solid tumors reported SD for 4/11 patients with previously treated colorectal cancer (CRC), 2 of whom experienced SD for >6 months[306]. Another Phase 2 basket trial of T-DM1 did not observe objective responses in any of 7 patients with ERBB2+ CRC, with 2 RAS wildtype patients receiving treatment for 6-8 months[307]. In case studies, a patient with RAS/BRAF wildtype, ERBB2+ metastatic CRC who had rapidly progressed on 2 lines of standard therapy experienced symptomatic clinical benefit and objective disease control for 7 months on T-DM1[127]. A second patient with KRAS-mutated, ERBB2+ metastatic CRC who had progressed on 4 prior treatment lines, including trastuzumab combined with the HER2/ERBB3 dimerization inhibitor pertuzumab, experienced short-term SD and regression of lung metastases from T-DM1[322]. Patients with HER2+ RAS/BRAF wildtype chemorefractory metastatic CRC achieved an ORR of 9.7% (3/31), SD rate of 68% (21/31), and a median PFS of 4.1 months on T-DM1 combined with pertuzumab in a Phase 2 trial[323].

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Fam-trastuzumab deruxtecan is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface and delivers the cytotoxic payload DXd, which inhibits DNA topoisomerase I to induce DNA damage. Fam-trastuzumab deruxtecan is FDA approved to treat patients with HER2-positive breast cancer and gastric or gastroesophageal junction adenocarcinoma who have received prior HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in solid cancers, including breast[80,324] , gastric[325-326] , non-small cell lung[327-328] , and colon[329] cancers, ERBB2 amplification may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

In the Phase 2 DESTINY-CRC01 trial, patients with HER2-positive, RAF/BRAF-wild-type, metastatic CRC achieved 45% (24/53) ORR, 83% (44/53) DCR, 6.9-month median PFS, and 15.5-month median OS with fam-trastuzumab deruxtecan; benefit was also observed for patients with prior HER2-targeted therapy (44% [7/16] ORR)[330-331] . No responses were reported for patients with lower HER2-expression defined by IHC2+/ISH- or IHC1+[331]. In a Phase 1 study evaluating single-agent fam-trastuzumab deruxtecan, patients with ERBB2-expressing or -mutated CRC experienced a 5% (1/20) ORR and an 80% DCR, with a median PFS of 4.0 months[332]. Fam-trastuzumab deruxtecan has demonstrated activity in multiple ERBB2-positive cancer types. In the Phase 2 DESTINY trials, clinical benefit was observed for patients treated with fam-trastuzumab deruxtecan monotherapy who had previously treated, HER2-expressing breast (60.9% ORR, median PFS 16.4 months)[80], colorectal (45.3% ORR, median PFS 6.9 months)[330], or gastric or gastroesophageal cancer (42.8% ORR, median PFS 5.6 months)[326], as well as HER2-mutated lung cancer (61.9% ORR, median PFS 14.0 months)[333]. In a Phase 1 study evaluating single-agent fam-trastuzumab deruxtecan for the treatment of patients with ERBB2-mutated solid tumors or ERBB2-expressing solid tumors other than breast or gastric cancer, the median PFS was 7.2 months and the ORR was 28.3% (17/60), with responses reported for patients with non-small cell lung carcinoma, breast cancer, colorectal cancer, salivary gland carcinoma, cholangiocarcinoma, and endometrial cancer[332].

Margetuximab

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Margetuximab is an Fc-engineered antibody targeting ERBB2/HER2 that was designed to enhance the anti-tumor immune response. Margetuximab is FDA approved for the treatment of patients with HER2-positive breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification may predict sensitivity to margetuximab[334-337] .

SUPPORTING DATA

In a Phase 1 basket trial of margetuximab in HER2-positive tumors, no responses were reported for 5 patients with colorectal cancer[335]. The Phase 3 SOPHIA trial of margetuximab for HER2+ metastatic breast cancer reported improved median PFS (5.8 vs. 4.9 months, HR=0.76) and ORR (22% vs. 16%) when combining margetuximab with chemotherapy, compared with trastuzumab and chemotherapy, for patients who had progressed on ≥2 prior HER2-directed therapies[334]; however, median OS was not statistically different between the 2 treatment arms (21.6 vs. 21.9 months, HR=0.62)[338]. In a Phase 1 trial for HER2-overexpressing solid tumors, 12% (7/60) of patients, including 4 with breast, 2 with gastroesophageal, and 1 with lacrimal gland cancers, experienced PRs, and a further 52% (31/60) of the cohort experienced SD[335]. In a study of margetuximab for HER2+ cancers, a patient with salivary gland cancer reported a PR[336].

Trastuzumab

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved as monotherapy and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma. Trastuzumab biosimilars are also FDA approved for these indications. Please see the drug label(s) for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[69-70,74,89,339-343] .

SUPPORTING DATA

The Phase 2 HERACLES-A trial evaluated trastuzumab plus lapatinib treatment in patients with HER2-positive, KRAS-wildtype colorectal cancer (CRC) and reported an ORR of 28% (9/32), with 1 patient achieving a CR and 8 patients achieving PR at the 6.7 year follow-up[111,344] . Preliminary results from the Phase 2a HER2-FUSCC-G study of the combination trastuzumab and pyrotinib for patients with HER2-positive metastatic CRC reported an ORR of 45% (5/11), median PFS (mPFS) of 7.8 months, and median OS (mOS) of 15 months; patients with wildtype RAS experienced improved survival outcomes when compared with those with RAS mutations[345]. Preliminary results from the Phase 2 MOUNTAINEER trial of the HER2 inhibitor tucatinib in combination with trastuzumab for ERBB2-amplified metastatic CRC reported an ORR of 55% (12/22), mPFS of 6.2 months, and mOS of 17.3 months[346]. A patient with ERBB2-amplified CRC treated with trastuzumab monotherapy in the first-line setting was reported to achieve a PR[347]. Identification of ERBB2 amplification in a case of advanced CRC resulted in treatment with a combination of trastuzumab and capecitabine/oxaliplatin, where the patient reported SD/minor response for 1 year[348].

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. These therapies are FDA approved in combination for the treatment of patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to trastuzumab in combination with pertuzumab[76,341,349-353] .

SUPPORTING DATA

Phase 2 trials investigating the combination of pertuzumab and trastuzumab for HER2-positive (amplification or overexpression) metastatic CRC refractory to standard treatment reported ORRs of 25.0% to 34.4% (7/28; 22/84; 11/32), DCR of 43.9% to 62.5% (25/57; 14/28; 20/32), median PFS of 2.9 to 4.0 months, and median OS of 11.5 to 25.0 months[77,336,354-355] . KRAS-wild-type compared with KRAS-mutated status was associated with improved ORR (39.5% [17/43] vs. 7.7% [1/13]), median PFS (5.3 vs. 1.4 months), and median OS (14.0 vs. 8.5 months) in one study[77].

Trastuzumab + Tucatinib

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and tucatinib is a reversible TKI targeting ERBB2/HER2. These therapies are FDA approved in combination for the treatment of patients with previously treated advanced HER2-positive breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in breast cancer[81-84] and colorectal cancer[346], ERBB2 amplification may predict sensitivity to trastuzumab plus tucatinib.

SUPPORTING DATA

Preliminary results from the Phase 2 MOUNTAINEER trial of trastuzumab in combination with tucatinib for patients with ERBB2-amplified metastatic CRC reported an ORR of 54.5% (12/22), median PFS of 6.2 months, and median OS of 17.3 months[346].

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 Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

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

GENE
APC

ALTERATION
Q1447*

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

NCT03833700

PHASE 1

A Study of E7386 in Participants With Advanced Solid Tumor Including Colorectal Cancer (CRC)

TARGETS
CBP, Beta-catenin

LOCATIONS: Fukuoka (Japan), Nagaizumi-cho (Japan), Chuo Ku (Japan), Kashiwa (Japan)

NCT05091346

PHASE 1/2

A Study of E7386 in Combination With Pembrolizumab in Previously Treated Participants With Selected Solid Tumors

TARGETS
CBP, Beta-catenin, PD-1

LOCATIONS: Osaka (Japan), Tokyo (Japan), Chiba-shi (Japan), Kashiwa (Japan), California

NCT04008797

PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Osakasayama (Japan), Chuo-Ku (Japan), Chiba (Japan), Kashiwa (Japan)

NCT03264664

PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS
CBP, Beta-catenin

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

GENE
ERBB2

ALTERATION
amplification - equivocal

RATIONALE
ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors. Tyrosine kinase inhibitors such as erlotinib, gefitinib, afatinib, and lapatinib have yielded limited clinical efficacy as monotherapies in CRC, suggesting that antibody therapeutics or combination therapies may be more beneficial in this tumor type.

NCT03843749

PHASE NULL

Pyrotinib in Combination With Trastuzumab in Treatment-refractory, HER2-positive Metastatic Colorectal Cancer.

TARGETS
EGFR, ERBB2

LOCATIONS: Shanghai (China)

NCT04380012

PHASE 2

A Clinical Study of Pyrotinib in Patients With HER2-positive Advanced Colorectal Cancer

TARGETS
EGFR, ERBB2

LOCATIONS: Hangzhou (China)

NCT04960943

PHASE 2

Efficacy and Safety of Pyrotinib in HER2 Positive Gastrointestinal Tumors

TARGETS
EGFR, ERBB2

LOCATIONS: Shanghai (China)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Seoul (Korea, Republic of), Chuo-ku (Japan), Koto-ku (Japan), Melbourne (Australia), Warszawa (Poland), Gdynia (Poland), Grzepnica (Poland), Budapest (Hungary), Brno (Czechia), Padova (Italy)

NCT04162327

PHASE 1

A Phase Ia/Ib Study of IBI315 in Patients With HER2-expressing Advanced Solid Tumor

TARGETS
ERBB2, PD-1

LOCATIONS: Beijing (China)

NCT04040699

PHASE 1

KN026 Combined With KN046 in Subjects With HER2 Positive Solid Tumor

TARGETS
ERBB2, CTLA-4, PD-L1

LOCATIONS: Beijing (China)

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

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

LOCATIONS: Alaska, Washington, Oregon, California, Idaho

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, ROS1, AXL, TRKA, MET, TRKC, CDK4, CDK6, FLT3, CSF1R, KIT, RET, mTOR, EGFR, ERBB2, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

LOCATIONS: Vancouver (Canada), Kelowna (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

GENE
PIK3CA

ALTERATION
M1043V

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

NCT04589845

PHASE 2

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

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

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Osaka (Japan)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

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

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04317105

PHASE 1/2

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

TARGETS
PD-1, CTLA-4, PI3K

LOCATIONS: Toronto (Canada), Massachusetts, Texas, Virginia

NCT03006172

PHASE 1

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

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

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

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT03842228

PHASE 1

Copanlisib, Olaparib, and Durvalumab in Treating Patients With Metastatic or Unresectable Solid Tumors

TARGETS
PI3K, PD-L1, PARP

LOCATIONS: Massachusetts, Texas

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.

BRIP1
K240T

CDK12
F426Y and amplification

MLL2
S2614L

PDGFRA
E75*

PIM1
E135K

PTCH1
S1280L

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*	*TET2*	*TGFBR2*	*TIPARP*
TNFAIP3	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*
WT1	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*				

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV1*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*
KMT2A (MLL)	*MSH2*	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*
RAF1	*RARA*	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***
TMPRSS2								

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT

CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version 6.3.0

The median exon coverage for this sample is 780x

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Ciardiello et al., 2018; ESMO Abstract LBA-004
7. Parikh et al., 2021; DOI: 10.1038/s43018-021-00269-7
8. Fukuoka S, et al. J. Clin. Oncol. (2020) pmid: 32343640
9. Kim et al., 2020; DOI: 10.1016/j.annonc.2020.04.073
10. Zhang Y, et al. BMC Gastroenterol (2021) pmid: 34688262
11. Sinicrope FA, et al. J. Clin. Oncol. (2013) pmid: 24019539
12. Gavin PG, et al. Clin. Cancer Res. (2012) pmid: 23045248
13. Bertagnolli MM, et al. J. Clin. Oncol. (2009) pmid: 19273709
14. Van Cutsem E, et al. J. Clin. Oncol. (2009) pmid: 19451425
15. Ribic CM, et al. N. Engl. J. Med. (2003) pmid: 12867608
16. Sargent DJ, et al. J. Clin. Oncol. (2010) pmid: 20498393
17. Fallik D, et al. Cancer Res. (2003) pmid: 14522894
18. Guastadisegni C, et al. Eur. J. Cancer (2010) pmid: 20627535
19. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
20. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
21. Nature (2012) pmid: 22810696
22. Histopathology (2007) pmid: 17204026
23. Samowitz WS, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11535541
24. Elsaleh H, et al. Clin Colorectal Cancer (2001) pmid: 12445368
25. Brueckl WM, et al. Anticancer Res. () pmid: 12820457
26. Guidoboni M, et al. Am. J. Pathol. (2001) pmid: 11438476
27. Gryfe R, et al. N. Engl. J. Med. (2000) pmid: 10631274
28. Sinicrope FA, et al. Gastroenterology (2006) pmid: 16952542
29. Laghi L, et al. Dig Dis (2012) pmid: 22722556
30. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
31. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
32. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
33. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
34. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
35. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
36. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
37. Cristescu R, et al. Science (2018) pmid: 30309915
38. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
39. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
40. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
41. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
42. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
43. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
44. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
45. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
46. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
47. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
48. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
49. Schenker at al., 2022; AACR Abstract 7845
50. Legrand et al., 2018; ASCO Abstract 12000
51. Fabrizio DA, et al. J Gastrointest Oncol (2018) pmid: 30151257
52. Stadler ZK, et al. J. Clin. Oncol. (2016) pmid: 27022117
53. Shao C, et al. JAMA Netw Open (2020) pmid: 33119110
54. Schwartz et al., 2018; ASCO Abstract 572
55. Innocenti F, et al. J Clin Oncol (2019) pmid: 30865548
56. Lee DW, et al. Clin Cancer Res (2019) pmid: 31285374
57. Randon G, et al. Eur J Cancer (2022) pmid: 34933155
58. Chen EX, et al. JAMA Oncol (2020) pmid: 32379280
59. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
60. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
61. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
62. Rizvi NA, et al. Science (2015) pmid: 25765070
63. Johnson BE, et al. Science (2014) pmid: 24336570
64. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
65. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
66. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
67. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
68. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
69. Slamon DJ, et al. N. Engl. J. Med. (2001) pmid: 11248153
70. Bang YJ, et al. Lancet (2010) pmid: 20728210
71. Chumsri S, et al. J Natl Compr Canc Netw (2015) pmid: 26358791
72. Cappuzzo F, et al. N. Engl. J. Med. (2006) pmid: 16775247
73. Falchook GS, et al. J Thorac Oncol (2013) pmid: 23328556
74. Mazières J, et al. J. Clin. Oncol. (2013) pmid: 23610105
75. Baselga J, et al. N. Engl. J. Med. (2012) pmid: 22149875
76. Swain SM, et al. N. Engl. J. Med. (2015) pmid: 25693012
77. Meric-Bernstam F, et al. Lancet Oncol. (2019) pmid: 30857956
78. Meric-Bernstam et al., 2019; ESMO Abstract 453PD
79. Verma S, et al. N. Engl. J. Med. (2012) pmid: 23020162
80. Modi S, et al. N. Engl. J. Med. (2019) pmid: 31825192
81. Murthy RK, et al. N. Engl. J. Med. (2020) pmid: 31825569
82. Borges VF, et al. JAMA Oncol (2018) pmid: 29955792
83. Murthy R, et al. Lancet Oncol. (2018) pmid: 29804905
84. Moulder SL, et al. Clin. Cancer Res. (2017) pmid: 28053022
85. Fan Y, et al. Mol Oncol (2020) pmid: 32478891
86. Cameron D, et al. Oncologist (2010) pmid: 20736298
87. Geyer CE, et al. N. Engl. J. Med. (2006) pmid: 17192538
88. Serra V, et al. Cancer Discov (2013) pmid: 23950206
89. Ali SM, et al. J. Clin. Oncol. (2014) pmid: 24516025
90. Grellety T, et al. Ann. Oncol. (2016) pmid: 26487584
91. Vornicova O, et al. Oncologist (2014) pmid: 25085898
92. Ronellenfitsch MW, et al. J Clin Invest (2020) pmid: 32017710
93. Hou JY, et al. Gynecol Oncol Rep (2020) pmid: 32405522
94. Lin NU, et al. Breast Cancer Res. Treat. (2012) pmid: 22418700
95. Schwab CL, et al. Br. J. Cancer (2014) pmid: 25268372
96. De Grève J, et al. Lung Cancer (2015) pmid: 25682316
97. De Grève J, et al. Lung Cancer (2012) pmid: 22325357
98. Li BT, et al. Lung Cancer (2015) pmid: 26559459
99. Dziadziuszko R, et al. J Thorac Oncol (2019) pmid: 30825613
100. Lai WV, et al. Eur. J. Cancer (2019) pmid: 30685684
101. Liu Z, et al. Onco Targets Ther (2018) pmid: 30425522
102. Fang W, et al. Oncologist (2019) pmid: 31748336
103. Yuan B, et al. Front Oncol (2020) pmid: 32477948
104. Ben-Baruch NE, et al. J Natl Compr Canc Netw (2015) pmid: 26358790
105. Ma CX, et al. Clin. Cancer Res. (2017) pmid: 28679771
106. Hyman DM, et al. Nature (2018) pmid: 29420467
107. Smyth LM, et al. Cancer Discov (2019) pmid: 31806627
108. Kris MG, et al. Ann. Oncol. (2015) pmid: 25899785
109. Jiang et al., 2019; ASCO Abstract 1001
110. Xu et al., 2020; ASCO Abstract 1003
111. Sartore-Bianchi A, et al. Lancet Oncol. (2016) pmid: 27108243
112. Siena S, et al. Lancet Oncol (2021) pmid: 33961795
113. Strickler et al., 2019; ESMO Abstract 527PD
114. Yuan et al., 2021; ASCO Abstract e15554
115. Liu et al., 2020; ASCO Abstract 1049
116. Johnsson A, et al. Ann. Oncol. (2013) pmid: 23788755
117. Ma BB, et al. Cancer (2013) pmid: 24114668
118. Frank D, et al. J Gastrointest Oncol (2012) pmid: 22811876
119. Bouche O, et al. Anticancer Res. (2011) pmid: 21737652
120. Bertotti A, et al. Cancer Discov (2011) pmid: 22586653
121. Siravegna G, et al. Nat. Med. (2015) pmid: 26030179
122. Yonesaka K, et al. Sci Transl Med (2011) pmid: 21900593
123. Pietrantonio F, et al. Clin. Cancer Res. (2017) pmid: 27780856
124. Jeong JH, et al. Clin Colorectal Cancer (2017) pmid: 28223103
125. Martin V, et al. Br. J. Cancer (2013) pmid: 23348520
126. Barry GS, et al. Oncotarget (2016) pmid: 26980732
127. Parikh A, et al. J Natl Compr Canc Netw (2017) pmid: 28040715
128. Knebel FH, et al. Cancers (Basel) (2020) pmid: 33322618
129. Takegawa N, et al. Oncotarget (2016) pmid: 26657506
130. Kavuri SM, et al. Cancer Discov (2015) pmid: 26243863
131. Sawada K, et al. Clin Colorectal Cancer (2018) pmid: 29866615
132. Gong J, et al. Oncotarget (2017) pmid: 28178681
133. Sartore-Bianchi A, et al. Oncologist (2019) pmid: 30952821
134. Ross JS, et al. Cancer (2018) pmid: 29338072
135. Ingold Heppner B, et al. Br. J. Cancer (2014) pmid: 25211663
136. Seo AN, et al. PLoS ONE (2014) pmid: 24879338
137. Sclafani F, et al. Ann. Oncol. (2013) pmid: 24146218
138. Wu SW, et al. Diagn Pathol (2015) pmid: 26276145
139. Higgins MJ, et al. J. Clin. Invest. (2011) pmid: 21965336
140. Van Cutsem E, et al. J. Clin. Oncol. (2011) pmid: 21502544
141. Bokemeyer C, et al. Ann. Oncol. (2011) pmid: 21228335
142. Karapetis CS, et al. N. Engl. J. Med. (2008) pmid: 18946061
143. De Roock W, et al. Ann. Oncol. (2008) pmid: 17998284
144. Douillard JY, et al. Ann. Oncol. (2014) pmid: 24718886
145. Douillard JY, et al. N. Engl. J. Med. (2013) pmid: 24024839
146. Amado RG, et al. J. Clin. Oncol. (2008) pmid: 18316791
147. Lièvre A, et al. Cancer Res. (2006) pmid: 16618717
148. De Roock W, et al. Lancet Oncol. (2011) pmid: 21163703
149. Chen J, et al. BMC Cancer (2014) pmid: 25367198
150. Li W, et al. BMC Cancer (2015) pmid: 25929517

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

151. Hu J, et al. Medicine (Baltimore) (2016) pmid: 27977612
152. Zekri J, et al. Genet. Mol. Res. (2017) pmid: 28218784
153. Staudacher JJ, et al. Clin Transl Gastroenterol (2017) pmid: 29048416
154. Wang Y, et al. Virchows Arch. (2018) pmid: 29705968
155. Guo F, et al. Sci Rep (2018) pmid: 29666387
156. Mármol I, et al. Int J Mol Sci (2017) pmid: 28106826
157. Kwak MS, et al. Medicine (Baltimore) (2017) pmid: 28858102
158. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
159. Kahn S, et al. Anticancer Res. () pmid: 3310850
160. Pentheroudakis G, et al. BMC Cancer (2013) pmid: 23374602
161. Vaughn CP, et al. Genes Chromosomes Cancer (2011) pmid: 21305640
162. Janku F, et al. Target Oncol (2013) pmid: 23400451
163. De Roock W, et al. Lancet Oncol. (2010) pmid: 20619739
164. Irahara N, et al. Diagn. Mol. Pathol. (2010) pmid: 20736745
165. Schirripa M, et al. Int. J. Cancer (2015) pmid: 24806288
166. Cercek A, et al. Clin. Cancer Res. (2017) pmid: 28446505
167. Zhan T, et al. Oncogene (2017) pmid: 27617575
168. Jung YS, et al. Exp Mol Med (2020) pmid: 32037398
169. Krishnamurthy N, et al. Cancer Treat Rev (2018) pmid: 29169144
170. Kawazoe et al., 2021; ESMO Abstract 473P
171. Yamada K, et al. Cancer Res (2021) pmid: 33408116
172. Kanda Y, et al. Biochem Biophys Res Commun (2022) pmid: 34837838
173. Christie M, et al. Oncogene (2013) pmid: 23085758
174. Quyn AJ, et al. Surgeon (2008) pmid: 19110823
175. Luke JJ, et al. Clin Cancer Res (2019) pmid: 30635339
176. Logan CY, et al. Annu. Rev. Cell Dev. Biol. (2004) pmid: 15473860
177. Eklof Spink K, et al. EMBO J. (2001) pmid: 11707392
178. Liu J, et al. J. Mol. Biol. (2006) pmid: 16753179
179. Dikovskaya D, et al. J. Cell. Sci. (2010) pmid: 20144988
180. Murphy SJ, et al. Dig. Dis. Sci. (2007) pmid: 17410430
181. Aretz S, et al. Hum. Mutat. (2004) pmid: 15459959
182. Kerr SE, et al. J Mol Diagn (2013) pmid: 23159591
183. Annu Rev Pathol (2011) pmid: 21090969
184. Kastritis E, et al. Int. J. Cancer (2009) pmid: 18844223
185. Half E, et al. Orphanet J Rare Dis (2009) pmid: 19822006
186. Fritsch C, et al. Mol. Cancer Ther. (2014) pmid: 24608574
187. Juric D, et al. J. Clin. Oncol. (2018) pmid: 29401002
188. Gallant JN, et al. NPJ Precis Oncol (2019) pmid: 30793038
189. Delestre F, et al. Sci Transl Med (2021) pmid: 34613809
190. Morschhauser F, et al. Mol Cancer Ther (2020) pmid: 31619463
191. Patnaik A, et al. Ann. Oncol. (2016) pmid: 27672108
192. Santin AD, et al. Gynecol Oncol Rep (2020) pmid: 31934607
193. Damodaran S, et al. J Clin Oncol (2022) pmid: 35133871
194. André F, et al. N. Engl. J. Med. (2019) pmid: 31091374
195. Smyth LM, et al. NPJ Breast Cancer (2021) pmid: 33863913
196. Park HS, et al. PLoS ONE (2016) pmid: 27105424
197. Lim SM, et al. Oncotarget (2016) pmid: 26859683
198. Hou MM, et al. Oncotarget (2014) pmid: 25426553
199. Varnier R, et al. Eur J Cancer (2019) pmid: 31351267
200. Janku F, et al. Cell Rep (2014) pmid: 24440717
201. Moroney J, et al. Clin. Cancer Res. (2012) pmid: 22927482
202. Basho RK, et al. JAMA Oncol (2017) pmid: 27893038
203. Moroney JW, et al. Clin. Cancer Res. (2011) pmid: 21890452
204. Zhao Y, et al. Cancer Res (2020) pmid: 32907836
205. Ng K, et al. Clin. Cancer Res. (2013) pmid: 23743569
206. Ganesan P, et al. Mol. Cancer Ther. (2013) pmid: 24092809
207. Brannon AR, et al. Genome Biol. (2014) pmid: 25164765
208. Huang L, et al. Arch Med Sci (2014) pmid: 24701207
209. Fong et al., 2022; ASCO GI Abstract 57
210. Samuels Y, et al. Cancer Cell (2005) pmid: 15950905
211. Nat. Rev. Cancer (2009) pmid: 19629070
212. Kang S, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15647370
213. Ikenoue T, et al. Cancer Res. (2005) pmid: 15930273
214. Gymnopoulos M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17376864
215. Horn S, et al. Oncogene (2008) pmid: 18317450
216. Rudd ML, et al. Clin. Cancer Res. (2011) pmid: 21266528
217. Hon WC, et al. Oncogene (2012) pmid: 22120714
218. Burke JE, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22949682
219. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915146
220. Laurenti R, et al. Rev Saude Publica (1990) pmid: 2103068
221. Dan S, et al. Cancer Res. (2010) pmid: 20530683
222. Oda K, et al. Cancer Res. (2008) pmid: 18829572
223. Zhao L, et al. Oncogene (2008) pmid: 18794883
224. Lui VW, et al. Cancer Discov (2013) pmid: 23619167
225. Ross RL, et al. Oncogene (2013) pmid: 22430209
226. Rivière JB, et al. Nat. Genet. (2012) pmid: 22729224
227. Shibata T, et al. Cancer Lett. (2009) pmid: 19394761
228. Dogruluk T, et al. Cancer Res. (2015) pmid: 26627007
229. Croessmann S, et al. Clin. Cancer Res. (2018) pmid: 29284706
230. Ng PK, et al. Cancer Cell (2018) pmid: 29533785
231. Spangle JM, et al. (2020) pmid: 32929011
232. Chen L, et al. Nat Commun (2018) pmid: 29636477
233. Jin N, et al. J Clin Invest (2021) pmid: 34779417
234. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
235. Perotti D, et al. Oncogene (2008) pmid: 18391980
236. Ruteshouser EC, et al. Genes Chromosomes Cancer (2008) pmid: 18311776
237. Rivera MN, et al. Science (2007) pmid: 17204608
238. Major MB, et al. Science (2007) pmid: 17510365
239. Jenkins ZA, et al. Nat. Genet. (2009) pmid: 19079258
240. Perdu B, et al. J. Bone Miner. Res. (2010) pmid: 20209645
241. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
242. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
243. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
244. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
245. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
246. Xu L, et al. Mol. Med. (2001) pmid: 11713371
247. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
248. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
249. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
250. Hajdenberg et al., 2012; ASCO Abstract e15010
251. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
252. Moore et al., 2019; ASCO Abstract 5513
253. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
254. Oza et al., 2015; ASCO Abstract 5506
255. Lee J, et al. Cancer Discov (2019) pmid: 31315834
256. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
257. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
258. Kwok M, et al. Blood (2016) pmid: 26563132
259. Boudny M, et al. Haematologica (2019) pmid: 30975914
260. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
261. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
262. Goh HS, et al. Cancer Res. (1995) pmid: 7585578
263. Berg M, et al. PLoS ONE (2010) pmid: 21103049
264. Han SW, et al. PLoS ONE (2013) pmid: 23700467
265. Peeters M, et al. Clin. Cancer Res. (2013) pmid: 23325582
266. Malhotra P, et al. Tumour Biol. (2013) pmid: 23526092
267. Di Bartolomeo M, et al. Target Oncol (2014) pmid: 23821376
268. Wangefjord S, et al. Diagn Pathol (2013) pmid: 23337059
269. Russo A, et al. J. Clin. Oncol. (2005) pmid: 16172461
270. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
271. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
272. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
273. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
274. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
275. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
276. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
277. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
278. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
279. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
280. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
281. Lalloo F, et al. Lancet (2003) pmid: 12672316
282. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
283. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
284. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
285. Xie M, et al. Nat. Med. (2014) pmid: 25326804
286. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
287. Severson EA, et al. Blood (2018) pmid: 29678827
288. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
289. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
290. Chabon JJ, et al. Nature (2020) pmid: 32269342
291. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
292. Cunningham D, et al. N. Engl. J. Med. (2004) pmid: 15269313
293. Jonker DJ, et al. N. Engl. J. Med. (2007) pmid: 18003960
294. Raghav et al., 2019; DOI: 10.1200/PO.18.00226
295. Papamichael D, et al. Eur J Cancer (2022) pmid: 35033994
296. Karapetis CS, et al. Clin. Cancer Res. (2014) pmid: 24218517
297. Moiseyenko VM, et al. Clin Drug Investig (2018) pmid: 29470838
298. Stein A, et al. J Immunother Cancer (2021) pmid: 34315821
299. Price TJ, et al. Lancet Oncol. (2014) pmid: 24739896

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

300. Sakai D, et al. Eur J Cancer (2020) pmid: 32526634
301. Van Cutsem E, et al. J. Clin. Oncol. (2007) pmid: 17470858
302. Peeters M, et al. Clin. Cancer Res. (2015) pmid: 26341920
303. Kim TW, et al. Clin Colorectal Cancer (2018) pmid: 29703606
304. Shitara K, et al. Cancer Sci (2016) pmid: 27712015
305. Pietrantonio F, et al. JAMA Oncol (2019) pmid: 31268481
306. Jhaveri KL, et al. Ann. Oncol. (2019) pmid: 31504139
307. Li et al., 2018; ASCO Abstract 2502
308. Li BT, et al. Cancer Discov (2020) pmid: 32213539
309. Hotta K, et al. J Thorac Oncol (2018) pmid: 29313813
310. Krop IE, et al. Lancet Oncol. (2014) pmid: 24793816
311. Welslau M, et al. Cancer (2014) pmid: 24222194
312. Krop IE, et al. J. Clin. Oncol. (2012) pmid: 22649126
313. Burris HA, et al. J. Clin. Oncol. (2011) pmid: 21172893
314. Jhaveri et al., 2018; ASCO Abstract 100
315. Baselga J, et al. Clin. Cancer Res. (2016) pmid: 26920887
316. Perez EA, et al. J. Clin. Oncol. (2017) pmid: 28056202
317. Hurvitz SA, et al. J. Clin. Oncol. (2013) pmid: 23382472
318. von Minckwitz G, et al. N. Engl. J. Med. (2019) pmid: 30516102
319. Hurvitz SA, et al. J. Clin. Oncol. (2019) pmid: 31157583
320. Martin M, et al. Ann. Oncol. (2016) pmid: 27052654
321. Mondaca S, et al. JCO Precis Oncol (2019) pmid: 32923849
322. Sandhu J, et al. J Natl Compr Canc Netw (2020) pmid: 32023524
323. Sartore-Bianchi A, et al. ESMO Open (2020) pmid: 32988996
324. Tamura K, et al. Lancet Oncol. (2019) pmid: 31047803
325. Shitara K, et al. Lancet Oncol. (2019) pmid: 31047804
326. Shitara K, et al. N. Engl. J. Med. (2020) pmid: 32469182
327. Tsurutani et al., 2018; IASLC WCLC Abstract OA02.07
328. Nakagawa et al., 2021; WCLC Abstract OA04.05
329. Yoshino et al., 2018; ESMO Abstract 563P
330. Siena et al., 2020; ASCO Abstract 4000
331. Yoshino et al., 2021; ASCO Abstract 3505
332. Tsurutani J, et al. Cancer Discov (2020) pmid: 32213540
333. Smit et al., 2020; ASCO Abstract 9504
334. Rugo et al., 2019; ASCO Abstract 1000
335. Bang YJ, et al. Ann. Oncol. (2017) pmid: 28119295
336. Burris et al., 2013; ASCO Abstract 3004
337. Catenacci et al., 2019; ESMO Abstract 2812
338. Rugo et al., 2021; SABCS Abstract PD8-01
339. Gianni L, et al. Lancet Oncol. (2014) pmid: 24657003
340. Morris PG, et al. Cancer (2013) pmid: 24037735
341. Hainsworth JD, et al. J. Clin. Oncol. (2018) pmid: 29320312
342. Wang K, et al. Clin. Cancer Res. (2016) pmid: 27334835
343. Nishikawa K, et al. Int. J. Cancer (2017) pmid: 27521503
344. Tosi F, et al. Clin Colorectal Cancer (2020) pmid: 32919890
345. Li et al., 2022; ASCO GI Abstract 97
346. Strickler et al., 2019; ESMO Congress Abstract 527PD
347. Kratz et al., 2019; AACR Annual meeting Abstract 1414
348. Disel U, et al. Oncoscience (2015) pmid: 26244165
349. Hurvitz SA, et al. Lancet Oncol. (2018) pmid: 29175149
350. von Minckwitz G, et al. N. Engl. J. Med. (2017) pmid: 28581356
351. Swain SM, et al. Ann Oncol (2018) pmid: 29253081
352. Gianni L, et al. Lancet Oncol. (2016) pmid: 27179402
353. Shao Z, et al. JAMA Oncol (2020) pmid: 31647503
354. Gupta et al., 2020; ASCO GI Abstract 132
355. Nakamura et al., 2019; ESMO Congress Abstract 526PD

Electronically signed by Erik Williams, M.D. | 29 June 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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