FOUNDATIONONE®CDx

PATIENT
Shen, Li-Chen

TUMOR TYPE
Ovary clear cell carcinoma
COUNTRY CODE
TW

REPORT DATE
19 Jan 2022
ORDERED TEST #
ORD-1273826-01

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 Ovary clear cell carcinoma
NAME Shen, Li-Chen
DATE OF BIRTH 03 October 1976
SEX Female
MEDICAL RECORD # 42375304

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 Ovary
SPECIMEN ID S110-67626K (PF22001)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 30 September 2021
SPECIMEN RECEIVED 07 January 2022

Biomarker Findings

Loss of Heterozygosity score - 3.1%
Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

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

PIK3CA E545K
ARID1A D1850fs*4
ZNF217 amplification - equivocal†

2 Disease relevant genes with no reportable alterations: ***BRCA1, BRCA2***

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type: Everolimus** (p. 7), **Temsirolimus** (p. 7)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Loss of Heterozygosity score - 3.1%	**No therapies or clinical trials.** see Biomarker Findings section	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 1 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***PIK3CA* -** E545K	none	Everolimus
10 Trials *see p. 10*		Temsirolimus
***ARID1A* -** D1850fs*4	none	none
8 Trials *see p. 8*		

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

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of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

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

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BIOMARKER

Loss of Heterozygosity score

RESULT
3.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2]. In platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma, rucaparib elicited significantly longer median PFS (7.2 vs. 5.0 months, HR=0.51) and improved ORR (33.3% vs. 9.6%, p=0.0003) for patients with LOH score ≥ 16%[2]. In the maintenance setting in platinum-sensitive, BRCA1/2 wild-type patients, rucaparib was superior to placebo in both the LOH score ≥ 16% (median PFS, 9.7 vs. 5.4 months; HR=0.44) and LOH score < 16% (median PFS, 6.7 vs. 5.4 months; HR=0.58) cohorts[1]. Similar results have been reported for maintenance treatment with niraparib in ovarian cancer[3] when using a different measure of HRD that includes genomic LOH[4-5]. Increased LOH has also been associated with improved sensitivity to platinum-containing chemotherapy regimens in patients with ovarian or breast cancer[6-8].

FREQUENCY & PROGNOSIS

In a study of more than 4,000 ovarian, Fallopian tube, or peritoneal cancer samples, genomic LOH score ≥ 16% was identified in 24.2% of BRCA1/2 wild-type cases, deleterious BRCA1/2 mutation was identified in an additional 17.2% of cases, and the remaining 58.7% of cases had LOH score < 16% and were BRCA1/2 wild-type[9]. Among the histological subtypes, LOH score ≥ 16% or BRCA1/2 mutation was reported in 42.4% of serous carcinomas, 37.6% of endometrioid carcinomas, 23.5% of carcinosarcomas, 20.6% of neuroendocrine carcinomas, 13.6% of clear cell carcinomas, and 8.1% of mucinous carcinomas; in BRCA1/2 wild-type samples, the median LOH score was significantly higher in serous as compared with non-serous cases[9]. In ovarian carcinoma, the median LOH score is significantly higher for BRCA1/2-mutated cases than BRCA1/2 wild-type cases (22.2% vs. 9.8%)[9], and mutation or methylation of BRCA1, BRCA2, or RAD51C has been reported to be enriched in cases with increased genomic LOH[6,10]. One study reported no association between LOH and either tumor stage or grade in ovarian serous carcinoma[11]. In patients with high-grade serous ovarian carcinoma, the frequency of LOH has been reported to increase significantly with age[12].

FINDING SUMMARY

The loss of heterozygosity (LOH) score is a profile of the percentage of the tumor genome that is under focal loss of one allele[2]; focal LOH events accumulate as genomic "scars" as a result of incorrect DNA double-strand break repair when the homologous recombination pathway is deficient (HRD)[6,10,13-14]. HRD and consequent genomic LOH occur as a result of genetic or epigenetic inactivation of one or more of the homologous recombination pathway proteins, including BRCA1, BRCA2, RAD51C, ATM, PALB2, and BRIP1[13-16]. This sample harbors a genomic LOH score below levels that have been associated with improved rates of clinical benefit from treatment with the PARP inhibitor rucaparib in patients with platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma[2]. However, patients with lower genomic LOH have also responded to rucaparib, and this type of LOH score does not preclude benefit from PARP inhibitors[1-2].

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[17-19], including approved therapies nivolumab and pembrolizumab[20]. 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)[21].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been reported in 1.6-19.7% of ovarian cancer samples[22-23], including 3.8% (1/26) of ovarian endometrioid adenocarcinomas[24], and 10.0% (3/30) of ovarian clear cell carcinomas (CCOCs)[25]. No association of MSI-H with stage or survival was found in patients with ovarian cancer[22,26].

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[27]. 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[27-29]. 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[30-32]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[27,29,31-32].

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BIOMARKER

Tumor Mutational Burden

RESULT
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[33-35], anti-PD-1 therapies[33-36], and combination nivolumab and ipilimumab[37-42]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[33-36,43]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[33]. 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[44] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[34]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[36,43]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Ovarian clear cell carcinoma harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 1.7% of cases have high TMB (>20 muts/Mb)[45]. In a study of high grade serous ovarian cancer, homologous recombination (HR)-deficient tumors, which comprised ~50% of all samples, harbored a higher neoantigen load compared to HR-proficient tumors; higher neoantigen load was associated with longer OS but not disease free survival[46].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[47-48] and cigarette smoke in lung cancer[49-50], treatment with temozolomide-based chemotherapy in glioma[51-52], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[53-57], and microsatellite instability (MSI)[53,56-57]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[34-35,43].

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GENE
PIK3CA

ALTERATION
E545K

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
1633G>A

VARIANT ALLELE FREQUENCY (% VAF)
26.2%

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[58-60], AKT[61-62], or mTOR[63-70]. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[71]. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)[72]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)[73]. The PI3K inhibitor alpelisib demonstrated an ORR of 6.0% (8/134) and a DCR of 58% (78/134) in a study for patients with PIK3CA-mutated solid tumors[74]. However, the PI3K inhibitor copanlisib exhibited limited efficacy in PIK3CA-mutated tumors[75-76].

FREQUENCY & PROGNOSIS

PIK3CA mutation frequency is variable among different subtypes of ovarian cancer. Mutations were detected in 33% of clear cell carcinomas and in 12% of advanced epithelial ovarian carcinomas; however, PIK3CA mutations were detected in 3% of high-grade serous ovarian cancers and in fewer than 1% of tumors in the TCGA Ovarian Serous Cystadenocarcinoma dataset[15,77-79]. A study of ovarian clear cell carcinomas reported an association of coexistent alterations in ARID1A and PIK3CA with poor prognosis[80]. There are differing reports on the impact of PIK3CA alteration on prognosis in patients with ovarian carcinoma; PIK3CA mutation or overexpression was associated with favorable survival in patients with ovarian clear cell carcinoma[81-82], whereas PIK3CA amplification has been associated with higher grade ovarian tumors[83-85] and with shorter survival in patients with ovarian cancer in general[86-89].

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[90-91]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[92-112].

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GENE
ARID1A

ALTERATION
D1850fs*4

TRANSCRIPT ID
NM_006015

CODING SEQUENCE EFFECT
5548_5549insG

VARIANT ALLELE FREQUENCY (% VAF)
54.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[113]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[114]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[115]. In a Phase 1 trial, a patient with metastatic colorectal cancer harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[116]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[117-118], which are under investigation in clinical trials. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[119-121]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[122]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[123-124] and to 5-fluorouracil in colorectal cancer cell lines[125].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, Jan 2022)[126-134]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[24,122,135-137], CRC[122,138-140], and gastric cancer[122,141-145]. Several studies have reported no correlation between ARID1A loss and clinicopathological parameters in ovarian clear cell or endometrioid carcinomas or other endometrial cancers[146-149], whereas others suggest that ARID1A loss is a negative prognostic factor[124,150].

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[130,144,151-157]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[130,142,152-153,158], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
ZNF217

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available targeted therapies to address genomic alterations in ZNF217. Expression of ZNF217 may predict relapse of estrogen receptor (ER)-positive breast cancer under hormone therapy through its direct interaction with ER-alpha[159-160]. ZNF217 overexpression has also been associated with resistance to paclitaxel[161] and doxorubicin[162] in breast cancer cell lines. ZNF217 has been suggested as a potential biomarker for treatment with the DNA synthesis inhibitor and AKT inhibitor triciribine in breast cancer based on preclinical findings in cultured cells and xenografts expressing high levels of ZNF217; triciribine treatment also restored sensitivity to doxorubicin in these cells[163].

FREQUENCY & PROGNOSIS

Amplification and/or overexpression of ZNF217 has been reported in breast[164], ovarian[165-166], gastric[167-168], colon[169], prostate[170], esophageal[171], and urothelial carcinomas[172], glioblastoma[173], and ovarian carcinosarcomas[174]. Overexpression in these tumors has generally been linked with aggressive tumor behavior and poor clinical prognosis. High levels of ZNF217 expression result in dysregulation of a broad range of genes that may contribute to tumorigenesis[175-177], and increased expression or activation of ERBB3[164,178], FAK[164], Aurora kinase A[161], AKT[162], and TGF-beta/SMAD signaling[164] has been demonstrated in ZNF217-expressing tumors or cells.

FINDING SUMMARY

ZNF217 encodes a candidate oncogene that has likely roles in histone modification and transcriptional repression[162,179]. ZNF217 amplification has been correlated with protein overexpression in breast carcinoma tumors and cell lines[180]. The role of ZNF217 in promoting tumorigenesis was established in preclinical studies demonstrating that expression of ZNF217 results in the immortalization of both human mammary epithelial cells and ovarian surface epithelial cells in culture[181-182].

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Everolimus

Assay findings association

PIK3CA
E545K

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[63-70] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[67-70,183-187] .

SUPPORTING DATA

A Phase 1 clinical trial of everolimus in combination with bevacizumab and panitumumab in patients with advanced solid tumors reported long-term disease control in three patients with ovarian cancer[188]. In a Phase 1 clinical trial of everolimus in combination with chemotherapy regimens in patients with solid tumors, complete responses were experienced by 2/27 patients, including one patient with primary peritoneal carcinoma and one patient with pancreatic cancer, and partial responses were experienced by 3 additional patients[189]. However, a Phase 2 trial of 150 patients with primary peritoneal cancer, epithelial ovarian cancer, or Fallopian tube cancer reported that the addition of everolimus to bevacizumab did not significantly increase overall patient survival, and may have contributed to reduced therapy tolerability[190]. A case study of a patient with platinum-resistant recurrent ovarian clear cell carcinoma reported achievement of stable disease in response to everolimus monotherapy[191]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[192], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[193].

Temsirolimus

Assay findings association

PIK3CA
E545K

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[63-70] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[67-70,183-187] .

SUPPORTING DATA

Phase 2 studies have reported limited efficacy for single-agent temsirolimus in genomically unselected recurrent or platinum-refractory ovarian cancer; 24% (13/54) of patients experienced progression-free survival (PFS) for 6 months or more[194-195] . A Phase 2 study of temsirolimus in ovarian clear cell carcinoma (OCCC) reported responses in 14% (3/22) of patients treated with single-agent temsirolimus; in addition, 5% (1/21) complete response (CR), 10% (2/21) partial response (PR), and 29% (6/21) stable disease (SD) lasting more than 3 months were reported in patients treated with temsirolimus in combination with trabectedin[196]. Treatment of OCCC with temsirolimus in combination with carboplatin and paclitaxel followed by temsirolimus consolidation therapy elicited an ORR of 63% (19/30), median PFS of 12 months, and median overall survival of 25 months[197]. A Phase 1 trial of temsirolimus combined with liposomal doxorubicin and bevacizumab in patients with breast and gynecological malignancies reported 1% (1/74) CR, 19% (14/74) PR, and 18% (13/74) SD rates[70]. A Phase 1 study of temsirolimus in combination with bevacizumab reported that 62% (8/13) of patients with ovarian or primary peritoneal serous carcinoma achieved SD for more than 6 months[198]. Combination therapy with paclitaxel, bevacizumab, and temsirolimus in advanced solid tumors achieved 1 PR lasting 6 months and 1 SD lasting 18 months for ovarian cancer[199].

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

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

GENE

ARID1A

ALTERATION

D1850fs*4

RATIONALE

ARID1A loss or inactivation may predict sensitivity to ATR inhibitors. On the basis of preclinical evidence, ARID1A loss or inactivation may predict sensitivity to EZH2 inhibitors.

NCT02264678

PHASE 1/2

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

TARGETS ATR, PARP, PD-L1

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

NCT02630199

PHASE 1

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

TARGETS ATR

LOCATIONS: Seoul (Korea, Republic of)

NCT04104776

PHASE 1/2

A Study of CPI-0209 in Patients With Advanced Solid Tumors

TARGETS EZH2, TOP1

LOCATIONS: Washington, Michigan, Ohio, Massachusetts, New Jersey, Texas, Virginia, Georgia

NCT04266912

PHASE 1/2

Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors

TARGETS ATR, PD-L1

LOCATIONS: Texas

NCT03641547

PHASE 1

M6620 Plus Standard Treatment in Oesophageal and Other Cancer

TARGETS ATR

LOCATIONS: Glasgow (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom), Cardiff (United Kingdom)

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NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT02595931

PHASE 1

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

TARGETS
ATR

LOCATIONS: California, Missouri, Pennsylvania, Massachusetts, Connecticut, Tennessee, Florida

NCT04514497

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
ATR, TOP1

LOCATIONS: Arizona, Oklahoma, Missouri, Connecticut, Tennessee

GENE

PIK3CA

ALTERATION

E545K

RATIONALE

PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

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

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)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT02688881

PHASE 4

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

TARGETS
mTOR

LOCATIONS: Seoul (Korea, Republic of)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

Electronically signed by Erik Williams, M.D. | 19 January 2022
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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)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Alaska, Washington

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, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Alaska, Washington, Oregon, California, Montana

NCT03648489

PHASE 2

Dual mTorc Inhibition in advanCed/Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer (of Clear Cell, Endometrioid and High Grade Serous Type, and Carcinosarcoma)

TARGETS
mTORC1, mTORC2

LOCATIONS: Berlin (Germany), Dresden (Germany), Essen (Germany), Sheffield (United Kingdom), Nottingham (United Kingdom), Lancaster (United Kingdom), Barrow In Furness (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Northwood (United Kingdom)

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NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ALK R510W	***APC*** V1125A	***CREBBP*** Q278P	***DAXX*** L500P
ERBB2 amplification†	***NOTCH3*** R1175W	***NTRK1*** R220W	***PARP1*** G974R
ROS1 N324S	***RPTOR*** V1182M	***SETD2*** H2249R	***TEK*** G743A
TSC1 Q654E and R86H	***TSC2*** V789I		

† *An* ERBB2 *amplification of copy number 4 was detected. While this result is considered a variant of unknown significance across tumor types, in a clinical concordance study of breast cancer samples with an FDA-approved FISH test, 70% (7 out of 10 samples) with copy number 4 were positive with an average ratio of 2.3, and 30% (3 out of 10) samples were negative by the FISH test.*

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

MR Suite Version 5.2.0

The median exon coverage for this sample is 837x

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

1. Coleman RL, et al. Lancet (2017) pmid: 28916367
2. Swisher EM, et al. Lancet Oncol. (2017) pmid: 27908594
3. Mirza MR, et al. N. Engl. J. Med. (2016) pmid: 27717299
4. Telli ML, et al. Clin. Cancer Res. (2016) pmid: 26957554
5. Timms KM, et al. Breast Cancer Res. (2014) pmid: 25475740
6. Wang ZC, et al. Clin. Cancer Res. (2012) pmid: 22912389
7. Telli ML, et al. J. Clin. Oncol. (2015) pmid: 25847929
8. Isakoff SJ, et al. J. Clin. Oncol. (2015) pmid: 25847936
9. Elvin et al., 2017; ASCO Abstract 5512
10. Abkevich V, et al. Br. J. Cancer (2012) pmid: 23047548
11. Marquard AM, et al. Biomark Res (2015) pmid: 26015868
12. Pedersen BS, et al. Genes Chromosomes Cancer (2013) pmid: 23716468
13. Watkins JA, et al. Breast Cancer Res. (2014) pmid: 25093514
14. Vanderstichele A, et al. Eur. J. Cancer (2017) pmid: 28950147
15. Nature (2011) pmid: 21720365
16. N. Engl. J. Med. (2003) pmid: 12736286
17. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
18. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
19. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
20. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
21. Ayers et al., 2016; ASCO-SITC Abstract P60
22. Segev Y, et al. Eur. J. Gynaecol. Oncol. (2015) pmid: 26775351
23. Plisiecka-Hałasa J, et al. Anticancer Res. () pmid: 18507046
24. Huang HN, et al. Histopathology (2015) pmid: 25195947
25. Strickland et al., 2016; ASCO Abstract 5514
26. Aysal A, et al. Am. J. Surg. Pathol. (2012) pmid: 22189970
27. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
28. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
29. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
30. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
31. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
32. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
33. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
34. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
35. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
36. Cristescu R, et al. Science (2018) pmid: 30309915
37. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
38. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
39. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
40. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
41. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
42. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
43. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
44. Legrand et al., 2018; ASCO Abstract 12000
45. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
46. Strickland KC, et al. Oncotarget (2016) pmid: 26871470
47. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
48. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
49. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
50. Rizvi NA, et al. Science (2015) pmid: 25765070
51. Johnson BE, et al. Science (2014) pmid: 24336570
52. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
53. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
54. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
55. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
56. Nature (2012) pmid: 22810696
57. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
58. Fritsch C, et al. Mol. Cancer Ther. (2014) pmid: 24608574
59. Juric D, et al. J. Clin. Oncol. (2018) pmid: 29401002
60. Gallant JN, et al. NPJ Precis Oncol (2019) pmid: 30793038
61. André F, et al. N. Engl. J. Med. (2019) pmid: 31091374
62. Smyth LM, et al. NPJ Breast Cancer (2021) pmid: 33863913
63. Park HS, et al. PLoS ONE (2016) pmid: 27105424
64. Lim SM, et al. Oncotarget (2016) pmid: 26859683
65. Hou MM, et al. Oncotarget (2014) pmid: 25426553
66. Varnier R, et al. Eur J Cancer (2019) pmid: 31351267
67. Janku F, et al. Cell Rep (2014) pmid: 24440717
68. Moroney J, et al. Clin. Cancer Res. (2012) pmid: 22927482
69. Basho RK, et al. JAMA Oncol (2017) pmid: 27893038
70. Moroney JW, et al. Clin. Cancer Res. (2011) pmid: 21890452
71. Krop et al., 2018; ASCO Abstract 101
72. Pascual J, et al. Cancer Discov (2021) pmid: 32958578
73. Dolly SO, et al. Clin. Cancer Res. (2016) pmid: 26787751
74. Aust Fam Physician (1986) pmid: 2941002
75. Santin AD, et al. Gynecol Oncol Rep (2020) pmid: 31934607
76. Patnaik A, et al. Ann. Oncol. (2016) pmid: 27672108
77. Kuo KT, et al. Am. J. Pathol. (2009) pmid: 19349352
78. Levine DA, et al. Clin. Cancer Res. (2005) pmid: 15837735
79. Matulonis UA, et al. PLoS ONE (2011) pmid: 21931712
80. Uehara Y, et al. PLoS ONE (2015) pmid: 26043110
81. Rahman M, et al. Hum. Pathol. (2012) pmid: 22705003
82. Abe A, et al. Hum. Pathol. (2013) pmid: 22955107
83. Carden CP, et al. Mol. Cancer Ther. (2012) pmid: 22556379
84. Kolasa IK, et al. Cancer Biol. Ther. (2009) pmid: 19029838
85. Nakayama K, et al. Int. J. Cancer (2007) pmid: 17351921
86. Kato S, et al. Int. J. Cancer (2007) pmid: 17590872
87. Woenckhaus J, et al. Virchows Arch. (2007) pmid: 17377809
88. Niskakoski A, et al. Int. J. Cancer (2013) pmid: 23716351
89. Huang J, et al. Genes Chromosomes Cancer (2011) pmid: 21563232
90. Samuels Y, et al. Cancer Cell (2005) pmid: 15950905
91. Nat. Rev. Cancer (2009) pmid: 19629070
92. Kang S, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15647370
93. Ikenoue T, et al. Cancer Res. (2005) pmid: 15930273
94. Gymnopoulos M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17376864
95. Horn S, et al. Oncogene (2008) pmid: 18317450
96. Rudd ML, et al. Clin. Cancer Res. (2011) pmid: 21266528
97. Hon WC, et al. Oncogene (2012) pmid: 22120714
98. Burke JE, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22949682
99. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915146
100. Laurenti R, et al. Rev Saude Publica (1990) pmid: 2103068
101. Dan S, et al. Cancer Res. (2010) pmid: 20530683
102. Oda K, et al. Cancer Res. (2008) pmid: 18829572
103. Zhao L, et al. Oncogene (2008) pmid: 18794883
104. Lui VW, et al. Cancer Discov (2013) pmid: 23619167
105. Ross RL, et al. Oncogene (2013) pmid: 22430209
106. Rivière JB, et al. Nat. Genet. (2012) pmid: 22729224
107. Shibata T, et al. Cancer Lett. (2009) pmid: 19394761
108. Dogruluk T, et al. Cancer Res. (2015) pmid: 26627007
109. Croessmann S, et al. Clin. Cancer Res. (2018) pmid: 29284706
110. Ng PK, et al. Cancer Cell (2018) pmid: 29533785
111. Spangle JM, et al. (2020) pmid: 32929011
112. Chen L, et al. Nat Commun (2018) pmid: 29636477
113. Williamson CT, et al. Nat Commun (2016) pmid: 27958275
114. Aggarwal et al., 2021; ESMO Abstract 512O
115. Thomas A, et al. J. Clin. Oncol. (2018) pmid: 29252124
116. Yap TA, et al. J Clin Oncol (2020) pmid: 32568634
117. Bitler BG, et al. Nat. Med. (2015) pmid: 25686104
118. Kim KH, et al. Nat. Med. (2015) pmid: 26552009
119. Wiegand KC, et al. BMC Cancer (2014) pmid: 24559118
120. Huang HN, et al. Mod. Pathol. (2014) pmid: 24336158
121. Samartzis EP, et al. Oncotarget (2014) pmid: 24979463
122. Okamura R, et al. J Immunother Cancer (2020) pmid: 32111729
123. Yokoyama Y, et al. J Gynecol Oncol (2014) pmid: 24459582
124. Katagiri A, et al. Mod. Pathol. (2012) pmid: 22101352
125. Xie C, et al. Tumour Biol. (2014) pmid: 24833095
126. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
127. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
128. Gao J, et al. Sci Signal (2013) pmid: 23550210
129. Wu RC, et al. Cancer Biol. Ther. (2014) pmid: 24618703
130. Jones S, et al. Hum. Mutat. (2012) pmid: 22009941
131. Dulak AM, et al. Nat. Genet. (2013) pmid: 23525077
132. Streppel MM, et al. Oncogene (2014) pmid: 23318448
133. Jiao Y, et al. J. Pathol. (2014) pmid: 24293293
134. Ross JS, et al. Oncologist (2014) pmid: 24563076
135. Hussein YR, et al. Mod. Pathol. (2015) pmid: 25394778
136. Bosse T, et al. Mod. Pathol. (2013) pmid: 23702729
137. Allo G, et al. Mod. Pathol. (2014) pmid: 23887303
138. Chou A, et al. Hum. Pathol. (2014) pmid: 24925223
139. Ye J, et al. Hum. Pathol. (2014) pmid: 25311944
140. Wei XL, et al. World J. Gastroenterol. (2014) pmid: 25561809
141. Chen K, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25583476
142. Wang K, et al. Nat. Genet. (2011) pmid: 22037554
143. Abe H, et al. Virchows Arch. (2012) pmid: 22915242
144. Wang DD, et al. PLoS ONE (2012) pmid: 22808142
145. Wiegand KC, et al. Hum. Pathol. (2014) pmid: 24767857
146. Rahman M, et al. Hum. Pathol. (2013) pmid: 22939958
147. Maeda D, et al. Int J Mol Sci (2010) pmid: 21614196
148. Lowery WJ, et al. Int. J. Gynecol. Cancer (2012) pmid: 22193641
149. Fadare O, et al. Mod. Pathol. (2013) pmid: 23524907
150. Mao TL, et al. Am. J. Surg. Pathol. (2013) pmid: 24076775
151. Guan B, et al. Cancer Res. (2011) pmid: 21900401
152. Wiegand KC, et al. N. Engl. J. Med. (2010) pmid:

20942669
153. Jones S, et al. Science (2010) pmid: 20826764
154. Yan HB, et al. Carcinogenesis (2014) pmid: 24293408
155. Huang J, et al. Nat. Genet. (2012) pmid: 22922871
156. Chan-On W, et al. Nat. Genet. (2013) pmid: 24185513
157. Mamo A, et al. Oncogene (2012) pmid: 21892209
158. Zang ZJ, et al. Nat. Genet. (2012) pmid: 22484628
159. Nguyen NT, et al. Mol Oncol (2014) pmid: 24973012
160. Frietze S, et al. BMC Genomics (2014) pmid: 24962896
161. Thollet A, et al. Mol. Cancer (2010) pmid: 21059223
162. Huang G, et al. Hum. Mol. Genet. (2005) pmid: 16203743
163. Littlepage LE, et al. Cancer Discov (2012) pmid: 22728437
164. Vendrell JA, et al. Cancer Res. (2012) pmid: 22593193
165. Li J, et al. Int J Clin Exp Pathol (2014) pmid: 25031722
166. Rahman MT, et al. Anticancer Res. (2012) pmid: 22843878
167. Yang SH, et al. Clin. Cancer Res. (2005) pmid: 15701848
168. Shida A, et al. Anticancer Res. (2014) pmid: 25202062
169. Rooney PH, et al. J. Pathol. (2004) pmid: 15476264
170. Szczyrba J, et al. Int. J. Cancer (2013) pmid: 22815235
171. Geppert CI, et al. Br. J. Cancer (2014) pmid: 24853183
172. Toncheva D, et al. Tumour Biol. () pmid: 15897688
173. Mao XG, et al. Lab. Invest. (2011) pmid: 21483406
174. Schipf A, et al. Virchows Arch. (2008) pmid: 18193277
175. Quinlan KG, et al. Biochim. Biophys. Acta (2007) pmid: 17572303
176. Krig SR, et al. J. Biol. Chem. (2007) pmid: 17259635
177. Cowger JJ, et al. Oncogene (2007) pmid: 17130829
178. Krig SR, et al. Oncogene (2010) pmid: 20661224
179. Banck MS, et al. Epigenetics (2009) pmid: 19242095
180. Collins C, et al. Proc. Natl. Acad. Sci. U.S.A. (1998) pmid: 9671742
181. Nonet GH, et al. Cancer Res. (2001) pmid: 11245413
182. Li P, et al. Int. J. Cancer (2007) pmid: 17266044
183. Janku F, et al. Cancer Res. (2013) pmid: 23066039
184. Janku F, et al. J. Clin. Oncol. (2012) pmid: 22271473
185. Janku F, et al. Mol. Cancer Ther. (2011) pmid: 21216929
186. Moulder S, et al. Ann. Oncol. (2015) pmid: 25878190
187. Byeon et al., 2020; doi: 10.21037/tcr.2020.04.07
188. Vlahovic G, et al. Cancer Chemother. Pharmacol. (2012) pmid: 22638798
189. Costello BA, et al. Invest New Drugs (2014) pmid: 24740268
190. Tew et al., 2014; ASCO Abstract 5546
191. Takatori E, et al. Onco Targets Ther (2014) pmid: 24511239
192. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
193. Patterson et al., 2018; AACR Abstract 3891
194. Behbakht K, et al. Gynecol. Oncol. (2011) pmid: 21752435
195. Emons G, et al. Gynecol. Oncol. (2016) pmid: 26731724
196. Takano et al., 2015; ASCO Abstract 5583
197. Farley et al., 2016; ASCO Abstract 5531
198. Piha-Paul SA, et al. Oncotarget (2014) pmid: 24742900
199. Westin et al., 2016; ASCO Abstract 2573

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