FOUNDATIONONE®CDx

PATIENT
Chang, Shu-Mei

TUMOR TYPE
Uterus carcinosarcoma
COUNTRY CODE
TW

REPORT DATE
27 Dec 2021
ORDERED TEST #
ORD-1257210-01

**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** Uterus carcinosarcoma
**NAME** Chang, Shu-Mei
**DATE OF BIRTH** 08 August 1947
**SEX** Female
**MEDICAL RECORD #** 22542025

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** Uterus
**SPECIMEN ID** S110-22362 A (PF21066)
**SPECIMEN TYPE** Slide Deck
**DATE OF COLLECTION** 05 August 2021
**SPECIMEN RECEIVED** 13 December 2021

## Biomarker Findings

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

## Genomic Findings

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

***PIK3CA*** H1047L
***ARID1A*** T1649fs*49, Y762fs*1
***PTEN*** R130G
***CTCF*** E239fs*2
***MLL2*** Q3910_Q3911del

† See About the Test in appendix for details.

## Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Temsirolimus** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***MLL2*** **Q3910_Q3911del** (p. 8)

| BIOMARKER FINDINGS | THERAPY AND CLINICAL TRIAL IMPLICATIONS |
|---|---|
| **Microsatellite status -** MS-Stable | **No therapies or clinical trials.** see Biomarker Findings section |
| **Tumor Mutational Burden -** 0 Muts/Mb | **No therapies or clinical trials.** see Biomarker Findings section |

| GENOMIC FINDINGS | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|
| ***PIK3CA*** **-** H1047L | none | Temsirolimus 2A |
| **10 Trials** *see p. 13* | | Everolimus |
| ***ARID1A*** **-** T1649fs*49, Y762fs*1 | none | none |
| **8 Trials** *see p. 11* | | |
| ***PTEN*** **-** R130G | none | none |
| **10 Trials** *see p. 15* | | |

☐ *NCCN category*

## VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

*Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.*

***MLL2*** **-** Q3910_Q3911del ..... p. 8



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## GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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



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

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



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BIOMARKER

# Microsatellite status

**RESULT**
MS-Stable

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

## FREQUENCY & PROGNOSIS

In uterine carcinosarcoma, MSI at any level has been reported in 9.5% (2/21) of cases[6], and high MSI (MSI-H) has been observed in 5% (1/21) to 21% (6/28) of cases[6-9]. MSS has been reported in 73-89% of endometrial cancers[10-17]. A genomic profiling study of gynecologic carcinosarcoma (N=109) reported that MSI was predictive of improved PFS (HR=0.1937) and OS (HR=0.0937) in multivariate analysis[9]. Data regarding the role of MSI status on prognosis and survival in endometrial cancer are conflicting, with most studies finding no relationship between MSI-H endometrial cancers and survival[12-13,15,18-20], and one study predicting improved disease-free and disease-specific survival[11]. However, these studies often evaluated endometrial cancers of all FIGO stages together. Studies specifically analyzing early stage endometrial cancer have reported a correlation between MSI-H and decreased survival[12,16,21-22], thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

## 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[23]. 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[23-25]. 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[26-28]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[23,25,27-28].



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BIOMARKER

# Tumor Mutational Burden

**RESULT**
0 Muts/Mb

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[29-31], anti-PD-1 therapies[29-32], and combination nivolumab and ipilimumab[33-38]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[29-32,39]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[29]. 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[40] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[30]. 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[32,39]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

## FREQUENCY & PROGNOSIS

In one study of 22 gynecologic carcinosarcomas, the average mutation burden was 1.4 mutations/Mb; the four tumors with mutation in either MLH1 or MSH6 had the highest mutation burden in this study ranging from 29-191 mutations/Mb[41]. In the TCGA Uterine Corpus Endometrioid Carcinoma dataset, 7.3% of cases were ultramutated, 28% were hypermutated, and 65% of samples were considered to have a low mutation rate[10]. Another study evaluating TMB in endometrial adenocarcinomas reported that 24% of tumors had a mutational burden of 10.4-541 mut/Mb), whereas 76% had 0-10.3 mut/Mb[42]. One study found TMB level was not significantly associated with OS for patients with uterine carcinosarcoma[43]. Increased tumor mutational burden (TMB) in endometrial carcinoma has been correlated with POLE mutation and advanced high-grade endometrioid subtypes[10,17,44-45]. Ultramutated endometrial tumors (elevated TMB with POLE mutations) have also been associated with improved PFS[10]. The same study associated lower mutational burden, independent of PD-L1 status, in endometrial carcinomas with poorer prognosis[10]. For patients with advanced microsatellite-stable endometrial carcinoma not treated with immunotherapy, OS did not significantly differ between patients with TMB-high (≥10 Muts/Mb) and TMB-low (11.4 vs. 13.5 months, adjusted HR=1.15) in 1 study[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[10,53-56], and microsatellite instability (MSI)[10,55-56]. 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[30-31,39].



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GENE
# *PIK3CA*

**ALTERATION**
H1047L

**TRANSCRIPT ID**
NM_006218

**CODING SEQUENCE EFFECT**
3140A>T

**VARIANT ALLELE FREQUENCY (% VAF)**
48.4%

## 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[57-59], AKT[60-61], or mTOR[62-69]. 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[70]. 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)[71]. 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)[72]. 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[73]. However, the PI3K inhibitor copanlisib exhibited limited efficacy in PIK3CA-mutated tumors[74-75].

## FREQUENCY & PROGNOSIS

PI3K pathway alterations are frequent in gynecologic carcinosarcomas and have been reported in greater than half of all cases in one study[41]. PIK3CA mutations have been reported in 19-41% of gynecologic carcinosarcomas[41,76] and 8% of endometrial carcinosarcoma[77]. Published data investigating the prognostic implications of PIK3CA alterations in uterine carcinosarcoma are limited (PubMed, Jul 2021).

## 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[78-79]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[80-100].



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GENE
# *ARID1A*

**ALTERATION**
T1649fs*49, Y762fs*1

**TRANSCRIPT ID**
NM_006015, NM_006015

**CODING SEQUENCE EFFECT**
4945_4946insA, 2286delC

**VARIANT ALLELE FREQUENCY (% VAF)**
44.0%, 43.5%

## 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[101]. 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[102]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[103]. 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[104]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[105-106], 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[107-109]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[110]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[111-112] and to 5-fluorouracil in colorectal cancer cell lines[113].

## 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, 2021)[114-122]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[45,110,123-125], CRC[110,126-128], and gastric cancer[110,129-133]. ARID1A protein loss is associated with tumors of poor histological grade for many tumor types, including colorectal cancer (CRC)[126-128], cervical cancer[134-135], gastric cancer[129-133], urothelial carcinoma[136-138], ovarian and endometrial cancers[45,112,123-125,139-143], breast carcinoma[144-146], and clear cell renal cell carcinoma[147]; ARID1A mutation has been associated with poor outcomes for patients with cholangiocarcinoma[148-151]. However, prognostic data regarding patient survival are often mixed and conflicting.

## 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[118,132,145,152-157]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[118,130,153-154,158], whereas ARID1A missense mutations are mostly uncharacterized.



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GENE
## *PTEN*

**ALTERATION**
R130G

**TRANSCRIPT ID**
NM_000314

**CODING SEQUENCE EFFECT**
388C>G

**VARIANT ALLELE FREQUENCY (% VAF)**
95.2%

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[75,159-161]. Across various tissues, most clinical studies have not observed an association between PTEN deficiency and response to inhibitors of the PI3K-AKT-mTOR pathway. However, limited studies in prostate cancer[162-165], renal cell carcinoma[166], breast cancer[167-168], and colorectal cancer[169] have reported an association between PTEN deficiency and response to inhibitors targeting the PI3K-AKT-mTOR pathway. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[170-174], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[175], ovarian cancer[176], uterine leiomyosarcoma[177], and endometrial cancer[174] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[178-179].

### FREQUENCY & PROGNOSIS

PTEN alterations have been reported in 12.9% of endometrial carcinosarcomas and 6.7% (3/45) of ovarian carcinosarcoma cases analyzed in COSMIC (Apr 2021)[114]. PTEN mutations have been reported in up to 40% of uterine carcinosarcomas in the literature[180-181]. A study of gynecological carcinosarcomas, including 17 uterine cases and 5 ovarian cases, identified alterations activating the PI3K pathway in over half of the samples analyzed, including PTEN mutations in 41% (9/22) of cases[41]. PTEN mutation has been associated with endometrioid-type but not serous-type uterine carcinosarcomas in multiple studies[182-184]. Loss of PTEN expression has been reported in 39% (12/31) of primary uterine carcinosarcomas, and specifically in 64% (20/37) of the epithelial component and 47% (17/33) of the mesenchymal component[185]. In addition, loss of PTEN expression has also been found in 53% (10/17) of the epithelial component of metastatic tissue of uterine carcinosarcomas, but not in any of the five mesenchymal components studied[185]. Published data investigating the prognostic implications of PTEN alteration in carcinosarcomas are limited (PubMed, Apr 2021).

### FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[160]. Alterations such as seen here may disrupt PTEN function or expression[186-227].

### POTENTIAL GERMLINE IMPLICATIONS

One or more of the PTEN variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with hamartoma tumor syndrome (ClinVar, Sep 2021)[228]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[229-230]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[229,231]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[229]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
## *CTCF*

**ALTERATION**
E239fs*2

**TRANSCRIPT ID**
NM_006565

**CODING SEQUENCE EFFECT**
716_717delAG

**VARIANT ALLELE FREQUENCY (% VAF)**
48.1%

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

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

### FREQUENCY & PROGNOSIS

Somatic mutations in CTCF are infrequently reported in most cancers, but have been observed more commonly (24%) in uterine corpus endometrial carcinoma (cBioPortal, 2021)[115-116]; nearly half of the observed mutations were truncating, suggesting a tumor suppressor role for CTCF in this disease. In addition, CTCF has been found to act as a tumor suppressor in breast cancer cell line studies[232-233].

### FINDING SUMMARY

CTCF encodes an 11-zinc-finger protein that is implicated in a number of regulatory roles, including gene activation and repression, imprinting, insulation, methylation, and X chromosome inactivation[234]. CTCF plays a role in transcriptional regulation of a number of key cancer-associated genes, including the oncogene MYC[235] and tumor suppressor TP53[236], via maintenance of local DNA methylation status. The decreased expression levels of CTCF and/or BORIS, another 11-zinc-finger transcriptional regulator, were reported to be closely associated with global DNA methylation variability and decreased overall survival in epithelial ovarian cancer[237-238].



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GENE
# *MLL2*

**ALTERATION**
Q3910_Q3911del

**TRANSCRIPT ID**
NM_003482

**CODING SEQUENCE EFFECT**
11729_11734delAGCAAC

**VARIANT ALLELE FREQUENCY (% VAF)**
40.8%

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

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

## FREQUENCY & PROGNOSIS

MLL2 alterations are observed in a number of solid tumor contexts (COSMIC, 2021)[114], and are especially prevalent in lung squamous cell carcinoma (SCC)[239] and small cell lung carcinoma (SCLC)[240]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[241]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[242]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[243].

## FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[244]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[245]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[246].

## 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[247-252]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[251,253-254]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

# Everolimus

*Assay findings association*

**PIK3CA**
H1047L

## 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[62-69] , 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[66-69,255-259] .

## SUPPORTING DATA

Of 2 patients with PIK3CA-mutated uterine malignant mixed Mullerian tumor (MMMT) who received everolimus monotherapy in the ProfiLER study, 1 achieved PR for 4.6 months and 1 experienced progressive disease[65]. In a Phase 1 study of everolimus in combination with sorafenib, of the 22 enrolled patients with advanced solid tumors, the best response was SD lasting 168 days in a patient with uterine carcinosarcoma[260]. A patient with a mixed Mullerian tumor exhibited a PR in a Phase 1 trial of a rapamycin analog, deforolimus[261]. A study of the mTOR inhibitor ridaforolimus as a single agent reported no clinical response in 5 patients with uterine carcinosarcoma[262]. In a Phase 2 clinical trial of recurrent endometrial cancer, 43% (12/28) of patients reported SD at 8 weeks and 21% (6/28) of patients achieved clinical benefit at 20 weeks upon administration of everolimus monotherapy[263]. Combination with the aromatase inhibitor letrozole for the same disease population achieved an ORR of 31% (11/35), with 9 CRs[264]. Further addition of metformin to this regimen led to a clinical benefit rate (CR+PR+SD) of 67% (32/48), including PR in 29% (14/48) of cases; no significant difference was observed between cases with and without KRAS mutation[265]. Everolimus achieved PR or SD in 35% of patients with recurrent endometrial carcinoma; KRAS mutation was associated with reduced median PFS (3.1 vs. 1.0 months) and median OS (9.3 vs. 2.3 months)[266]. Another study investigating estrogen and/or progesterone receptor-positive gynecologic or breast malignancies featuring mutation or loss of genes in the PI3K-AKT-mTOR pathway, including PIK3CA, AKT1, or PTEN, observed SD in 17% (1/6) of patients with endometrial cancer following combined treatment with everolimus and anastrozole[267]. No response was seen in a patient with endometrial stromal sarcoma and Peutz-Jeghers Syndrome associated with a germline STK11 mutation treated with a combination of everolimus and anastrozole[268]. 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[269], 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[270].

# Temsirolimus

*Assay findings association*

**PIK3CA**
H1047L

## 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[62-69] , 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[66-69,255-259] .

## SUPPORTING DATA

A study of the mTOR inhibitor ridaforolimus as a single agent reported no clinical response in 5 patients with uterine carcinosarcoma[262]. A study of the combination of temsirolimus and topotecan was investigated in endometrial cancers, including 3 patients with carcinosarcoma, with 9/15 patients experiencing stable disease; however, this regimen was not well tolerated in patients who had previously received radiation therapy[271]. A Phase 2 clinical trial of temsirolimus in recurrent or metastatic endometrial cancer reported PR in 4/29 (14%) chemotherapy-naïve patients and 4% (1/25) of chemotherapy-treated patients, with SD reported in 69% (20/29) of chemotherapy-naïve patients and 48% (12/25) of chemotherapy-treated patients; however, response in this study was found to be independent of molecular markers of PI3K-AKT-mTOR pathway activation[272]. Another Phase 2 study of temsirolimus in patients with endometrial cancer reported PFS of >15 months in 6 patients and associated clinical benefit and longer PFS with mutation of AKT1 or CTNNB1, respectively[273]. Temsirolimus combined with carboplatin and paclitaxel achieved objective partial responses in 82% (9/11) of patients with endometrial cancer[274]. A Phase 2 trial of temsirolimus in combination with bevacizumab in patients with endometrial carcinoma reported clinical response in 25% of patients[275].

**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.

**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*

**RATIONALE**
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

**ALTERATION**
T1649fs*49, Y762fs*1

## 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)

## NCT04266912

**PHASE 1/2**

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

**TARGETS**
ATR, PD-L1

**LOCATIONS:** Texas

## NCT04497116

**PHASE 1/2**

Study of RP-3500 in Advanced Solid Tumors

**TARGETS**
ATR, PARP

**LOCATIONS:** Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee, Texas

## 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

## 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)

## 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

**GENE**
*PIK3CA*

**ALTERATION**
H1047L

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

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

## NCT03239015

**PHASE 2**

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

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

**LOCATIONS:** Shanghai (China)

## NCT02688881

**PHASE 4**

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

**TARGETS**
mTOR

**LOCATIONS:** Seoul (Korea, Republic of)

## NCT04803318

**PHASE 2**

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

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

**LOCATIONS:** Guangzhou (China)

## NCT03772561

**PHASE 1**

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

**TARGETS**
PARP, AKTs, PD-L1

**LOCATIONS:** Singapore (Singapore)

## NCT04801966

**PHASE NULL**

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

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

**LOCATIONS:** Melbourne (Australia)

## NCT03994796

**PHASE 2**

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

**TARGETS**
ALK, ROS1, TRKA, TRKB, TRKC, 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**
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

**LOCATIONS:** Alaska, Washington, Oregon, California, Montana

## NCT03297606

**PHASE 2**

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

## NCT03673787

**PHASE 1/2**

A Trial of Ipatasertib in Combination With Atezolizumab

**TARGETS**
AKTs, PD-L1

**LOCATIONS:** Sutton (United Kingdom)

**GENE**
## *PTEN*

**ALTERATION**
R130G

**RATIONALE**
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

### NCT04269200

**PHASE 3**

Durvalumab With or Without Olaparib as Maintenance Therapy After First-Line Treatment of Advanced and Recurrent Endometrial Cancer

**TARGETS**
PD-L1, PARP

**LOCATIONS:** Nakagami-gun (Japan), Shanghai (China), Guangdong (China), Hong Kong (Hong Kong), HKG (Hong Kong), Changchun (China), Wuhan (China), Kurume-shi (Japan), Gyeongsangnam-do (Korea, Republic of), Suwon (Korea, Republic of)

### NCT04716686

**PHASE 2**

Niraparib Monotherapy as Maintain and Recurrent Treatment of Endometrial Serous Carcinoma

**TARGETS**
PARP

**LOCATIONS:** Jinan (China)

### NCT04001569

**PHASE 1/2**

AZD8186 and Paclitaxel in Advanced Gastric Cancer

**TARGETS**
PI3K-beta

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

### 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

### NCT03772561

**PHASE 1**

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

**TARGETS**
PARP, AKTs, PD-L1

**LOCATIONS:** Singapore (Singapore)

### NCT04801966

**PHASE NULL**

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

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

**LOCATIONS:** Melbourne (Australia)

ORDERED TEST # ORD-1257210-01

CLINICAL TRIALS

## NCT03651206

**PHASE 2/3**

Recurrent Ovarian CarcinoSarcoma Anti-pd-1 Niraparib

**TARGETS**
PARP, PD-1

**LOCATIONS:** Lille (France), Besançon (France), Paris (France), Villejuif (France), Lyon (France), Caen (France), Marseille (France), Montpellier (France), Angers (France), Poitiers (France)

## NCT03994796

**PHASE 2**

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

**TARGETS**
ALK, ROS1, TRKA, TRKB, TRKC, 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**
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

**LOCATIONS:** Alaska, Washington, Oregon, California, Montana

## NCT04497116

**PHASE 1/2**

Study of RP-3500 in Advanced Solid Tumors

**TARGETS**
ATR, PARP

**LOCATIONS:** Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee, 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.

***CREBBP***
V1924M

***KDM5A***
M1489T

***MEN1***
A163T

***MSH3***
R1061G

***NOTCH1***
R955H



Electronically signed by Erik Williams, M.D. | 27 December 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

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)



Electronically signed by Erik Williams, M.D. | 27 December 2021
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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



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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 965x



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