FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Yeh, Hsiu-Chin	Peritoneum serous carcinoma	18 Jan 2024
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1795940-01

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 Peritoneum serous carcinoma
NAME Yeh, Hsiu-Chin
DATE OF BIRTH 12 February 1970
SEX Female
MEDICAL RECORD # 27711633

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 Omentum
SPECIMEN ID S113-00200U (PF24006)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 03 January 2024
SPECIMEN RECEIVED 10 January 2024

Biomarker Findings

Loss of Heterozygosity score - 28.3%
Homologous Recombination status - HRD Positive
Microsatellite status - MS-Stable
Tumor Mutational Burden - 7 Muts/Mb

Genomic Findings

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

TP53 R196*
CDKN2A/B p16INK4a loss exon 1
KMT2A (MLL) 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 **NCCN categories of evidence** in this tumor type: **Olaparib** (p. 8), **Niraparib** (p. 7), **Rucaparib** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Loss of Heterozygosity score - 28.3%	Olaparib 1 Niraparib 2A Rucaparib 2A	Talazoparib
10 Trials see p. 11		
Homologous Recombination status - HRD Positive	HRD Positive defined as presence of deleterious *BRCA1/2* alteration and/or LOH score ≥ 16% (Coleman et al., 2017; 28916367).	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 7 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)
TP53 **-** R196*	none	none
2 Trials see p. 13		

NCCN category

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

BIOMARKER

Loss of Heterozygosity score

RESULT
28.3%

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[1-3]. 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%[1,3]. 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[2]. Similar results have been reported for maintenance treatment with niraparib in ovarian cancer[4] when using a different measure of HRD that includes genomic LOH[5-6]. Increased LOH has also been associated with improved sensitivity to platinum-containing chemotherapy regimens in patients with ovarian or breast cancer[7-9].

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[10]. 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[10]. 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%)[10], and mutation or methylation of BRCA1, BRCA2, or RAD51C has been reported to be enriched in cases with increased genomic LOH[7,11]. One study reported no association between LOH and either tumor stage or grade in ovarian serous carcinoma[12]. In patients with high-grade serous ovarian carcinoma, the frequency of LOH has been reported to increase significantly with age[13].

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[3]; 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)[7,11,14-15]. 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[14-17]. This sample harbors a genomic LOH score that has been shown to be associated with sensitivity to the PARP inhibitor rucaparib in platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma in both the treatment[1,3] and maintenance[2] settings.

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[18-20], including approved therapies nivolumab and pembrolizumab[21-22]. 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)[23].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been reported in 1.6-19.7% of ovarian cancer samples[24-25], including 3.8% (1/26) of ovarian endometrioid adenocarcinomas[26], and 10.0% (3/30) of ovarian clear cell carcinomas (CCOCs)[27]. No association of MSI-H with stage or survival was found in patients with ovarian cancer[24,28].

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 MMR in the tumor[29]. 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[29-31]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[32-34]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[29,31,33-34].

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BIOMARKER

Tumor Mutational Burden

RESULT
7 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[35-38], anti-PD-1 therapies[36-40], and combination nivolumab and ipilimumab[41-49]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[35-38,40,50-54]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[50]; similar findings were observed in the KEYNOTE 028 and 012 trials[40]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[54]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[55]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[53]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[35] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[37].

FREQUENCY & PROGNOSIS

Ovarian carcinomas, including peritoneal and Fallopian tube carcinomas, harbor a median TMB of 2.7-3.6 Muts/Mb depending upon subtype, and up to 2.1% of cases have high TMB (>20 Muts/Mb)[56]. 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[57].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitutions 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[58-59] and cigarette smoke in lung cancer[60-61], treatment with temozolomide-based chemotherapy in glioma[62-63], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[64-68], and microsatellite instability[64,67-68]. 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[37-38,50].

GENE
TP53

ALTERATION
R196*

HGVS VARIANT
NM_000546.4:c.586C>T (p.R196*)

VARIANT CHROMOSOMAL POSITION
chr17:7578263

VARIANT ALLELE FREQUENCY (% VAF)
62.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[69-72] or p53 gene therapy such as SGT53[73-78]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[79]. Phase 2 studies of adavosertib in combination with chemotherapy reported ORRs of 32% (30/94) and 41% (12/29) for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[80-81]. For patients with platinum-sensitive TP53-mutated ovarian cancer, the combination of adavosertib with paclitaxel and carboplatin significantly increased PFS compared with paclitaxel and carboplatin alone (9.9 vs. 8.0 months)[82]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[83]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[84]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[85]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[78]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[86]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[87].

FREQUENCY & PROGNOSIS

TP53 alterations have been reported in all subtypes of ovarian tumors; generally, high grade serous tumors are associated with greater frequency of TP53 alteration (>80%), while low grade serous and clear cell ovarian tumors are infrequently associated with TP53 alteration (<10%). The MSK-METropism study reported TP53 alterations in 96% of high grade serous ovarian cancers versus 1% in low grade serous and 15% of clear cell carcinomas, similar to trends reported across earlier studies[16,88-95]. Similarly, multiple genomic studies of ovarian mucinous neoplasms reported TP53 mutations in 12-18% of benign or borderline tumors and in 52-64% of carcinomas[96-97]. In endometrioid carcinomas, TP53 mutations were reported in 26% of cases in a genomic study[98]. Aberrant p53 expression has been associated with higher ovarian serous carcinoma grade (89-90% of high-grade vs. 6.6-9% of low-grade vs. 0% of benign)[99-101]. In one study, p53 expression was not prognostic in regard to outcome in patients with peritoneum serous carcinoma[102]. TP53 mutations have been reported to be more frequent in advanced stage (63%, 55/87) and higher grade (65%, 42/64) than earlier stage (31%, 14/45) and lower grade (41%, 7/17) ovarian carcinomas[93]. Meta-analysis has suggested that TP53 expression was associated with poorer survival in ovarian epithelial cancers, although the effect was modest and considerable variability was observed between studies[103].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[104]. Alterations such as seen here may disrupt TP53 function or expression[105-109].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 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 Li-Fraumeni syndrome (ClinVar, Sep 2023)[110]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[111-113], including sarcomas[114-115]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[116] to 1:20,000[115]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[117]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[118-123]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[118-119]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[124]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[122,125-126]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
CDKN2A/B

ALTERATION
p16INK4a loss exon 1

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[127-130]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[131] and palbociclib treatment[132-133]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[134-140]; it is not known whether CDK4/6 inhibitors would be beneficial in this case.

FREQUENCY & PROGNOSIS

CDKN2A mutation has been observed in <1% of peritoneal tumors analyzed in the COSMIC database (Jan 2023)[141]. In the Ovarian Serous Cystadenocarcinoma TCGA dataset, CDKN2A/B loss has been reported in 2.2% of cases, whereas mutations in these genes have not been detected[16]. Inactivation of CDKN2A/B by promoter methylation, leading to loss of p16INK4a and p15INK4b expression, has been reported in ovarian cancer samples[142-143]. Reduced expression of both CDKN2A mRNA and p16INK4a protein levels has been reported in 30% of epithelial ovarian tumors, but gene deletion accounted for very few to none of these cases[144-145]. Among low-grade tumors, loss of p16INK4a has been associated with the progression from borderline to low-grade invasive ovarian cancer, but p16INK4a expression in high-grade ovarian cancer has been reported to be variable[146]. Although earlier studies reported conflicting results on the association of p16INK4a expression and ovarian cancer prognosis[147-152], a large study of high-grade serous ovarian carcinoma concluded that homogeneous (high) p16INK4a expression and concurrent Rb positivity predict shorter patient survival[153].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[154-155]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[156-157]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[158-159]. One or more alterations observed here are predicted to result in p16INK4a loss of function[160-181].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[182]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[183-184]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[185-187]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[188-190]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
KMT2A (MLL)

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic mutations in or amplification of MLL.

FREQUENCY & PROGNOSIS

MLL amplification is rare in most solid tumors, occurring in <2% of cases in most tumor types (cBioPortal, Apr 2023)[191-192]. Published data investigating the prognostic implications of MLL alterations in ovarian, fallopian and peritoneal carcinomas are limited (PubMed, May 2023). Published data investigating the prognostic implications of KMT2A (MLL) alterations in solid tumors are limited (PubMed, Nov 2023).

FINDING SUMMARY

MLL (also known as KMT2A) encodes a histone methyltransferase, an enzyme involved in the modification of histones. It is involved in the positive regulation of transcription, particularly during development, although it is also expressed in most adult tissues[193-194]. MLL has been reported to be amplified in cancer, and may be biologically relevant in this context[195-197].

Niraparib

Assay findings association

Loss of Heterozygosity score
28.3%

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-3] . In platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma, the PARP inhibitor rucaparib elicited significantly longer median PFS and improved ORR for patients with LOH score ≥ 16%[1,3] .

SUPPORTING DATA

For patients with platinum-sensitive, recurrent ovarian cancer (OC), the Phase 3 ENGOT-OV16/NOVA study showed that niraparib maintenance therapy significantly increased median PFS (mPFS) relative to placebo, regardless of germline BRCA (gBRCA) mutation (21.0 vs. 5.5 months, HR=0.27 for patients with gBRCA mutations; 9.3 vs. 3.9 months, HR=0.45 for patients without gBRCA mutations) or homologous recombination deficiency (HDR) status (12.9 vs. 3.8 months, HR=0.38)[4,198] . Similarly, the Phase 3 PRIMA trial for patients with newly diagnosed advanced OC reported an extended mPFS from niraparib maintenance therapy after response to first-line platinum chemotherapy compared with placebo (13.8 vs. 8.2 months, HR=0.62); subgroup analysis showed that patients with HRD-positive OC experienced the longest mPFS, which was irrespective of BRCA mutational status (21.9 vs. 10.4 months, HR=0.43)[199]. The Phase 2 QUADRA study evaluating niraparib monotherapy as late-line treatment for patients with relapsed high-grade serous epithelial ovarian cancer (HGSOC) reported a median OS (mOS) of 12.2 months for all HGSOC patients, with highest mOS seen for those with BRCA1/2-mutated and HRD-positive tumors (26.0 and 19.0 months, respectively)[200]. A Phase 2 trial for patients with platinum-sensitive HGSOC and endometrioid recurrent ovarian cancer reported significantly improved mPFS from the addition of bevacizumab to niraparib compared with niraparib alone (11.9 vs. 5.5 months, HR=0.35)[201]. In a Phase 1/2 study of niraparib in combination with pembrolizumab for patients with recurrent platinum-resistant OC, patients experienced an ORR of 19% (11/59) and mPFS of 3.4 months; no significant differences in ORR were noted among analyzed subgroups: 14% (3/21) versus 19% (6/32) for patients with HRD-positive versus HRD-negative tumors, 18% (2/11) versus 19% (9/47) for patients with BRCA-mutated versus BRCA-wildtype tumors, and 21% (7/33) versus 10% (2/21) for patients with PD-L1-positive versus PD-L1-negative tumors[202].

Olaparib

Assay findings association

Loss of Heterozygosity score
28.3%

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-3] . In platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma, the PARP inhibitor rucaparib elicited significantly longer median PFS and improved ORR for patients with LOH score ≥ 16%[1,3] .

SUPPORTING DATA

Olaparib has been studied primarily to treat patients with ovarian cancer harboring BRCA1/2 mutations. Numerous Phase 2 studies have demonstrated significant clinical activity for patients with BRCA-mutated ovarian cancer, with response rates often significantly higher for patients with BRCA mutations than for those without[203-204] and for patients with platinum-sensitive (vs. platinum resistant) cancer[204-207] . As maintenance therapy for patients with newly diagnosed or platinum-sensitive relapsed ovarian cancer, olaparib monotherapy demonstrated significantly improved OS and median PFS (mPFS) compared with placebo in the Phase 3 SOLO-1 study[208] and multiple later-phase studies[209-213] . At the 7-year follow-up of SOLO-1, olaparib continued to improve mPFS compared with placebo for patients with ovarian cancer[214], and mOS was not reached for olaparib compared with 75.2 months for placebo (HR=0.55)[215]. In the first study of PARP inhibitor rechallenge for patients with ovarian cancer, the Phase 3 OReO/ENGOT Ov-38 study of maintenance olaparib compared with placebo reported statistically improved mPFS for both patients with BRCA-mutated (4.3 vs. 2.8 months, HR=0.57) and BRCA-unmutated (5.3 vs. 2.8 months, HR=0.43) cancer; in an exploratory analysis of the BRCA-unmutated cohort, improved mPFS was reported regardless of homologous recombination deficiency status[216]. The Phase 4 ORZORA trial confirmed the efficacy of olaparib as maintenance therapy for platinum-sensitive relapsed ovarian cancer after ≥2 lines of treatment, with an mPFS of 16.6 months for patients with somatic BRCA mutations (n=35) and of 19.3 months for those with germline BRCA mutations (n=52)[217]. Olaparib has been evaluated in combination with other therapies. A statistically superior median PFS (mPFS) from treatment with olaparib in combination with the VEGF inhibitor bevacizumab compared with bevacizumab monotherapy was reported in the Phase 3 PAOLA-1 study for patients with newly diagnosed advanced ovarian cancer in the intent-to-treat population (22.1 vs. 16.6 months, HR=0.59), in the population with BRCA1/2 mutations (37.2 vs. 21.7 months, HR=0.31), and in the population with wildtype BRCA1/2 harboring homologous recombination deficiency (HRD)-positive status (28.1 vs. 16.6 months, HR=0.43); however, no significant difference in mPFS was reported in the population with mutations in non-BRCA genes involved in homologous recombination repair (HRR) (16.8-22.1 vs. 16.6-27.0 months, HR=0.95-1.83)[218]. The final OS analysis for this trial reported benefit from the maintenance treatment using olaparib plus bevacizumab versus bevacizumab alone for patients with HRD-positive status (65.5 vs. 48.4 months), patients with HRD-positive status and BRCA1/2 mutations (73.2 vs. 53.8 months), and patients with HRD-positive status without BRCA1/2 mutations (54.7 vs. 44.2 months)[219]. For patients with platinum-sensitive recurrent ovarian cancer who previously progressed on chemotherapy, statistically increased mPFS was reported in a Phase 2 study of olaparib in combination with chemotherapy (12.2 months) compared with chemotherapy alone (9.6 months)[220], as well as from treatment with the VEGFR inhibitor cediranib compared with olaparib monotherapy in a Phase 1/2 trial[221]. Combination treatment with cediranib and olaparib also demonstrated numerically longer mPFS compared with chemotherapy alone for patients with BRCA1/2-mutated platinum-sensitive recurrent ovarian cancer (10.5 vs. 18 months); however, improved clinical benefit was not observed for patients without BRCA1/2 mutation (mPFS of 9.7 vs. 8.9 months) or for the overall intent-to-treat population (mPFS of 10.3 vs. 10.4 months, ORR of 71% vs. 69%)[222]. The Phase 2 CAPRI study for PARP inhibitor-resistant patients with HRD platinum-sensitive high-grade ovarian cancer treated with combination therapy of olaparib and the ATR inhibitor ceralasertib reported an ORR of 46% (n=13, 6 PRs) and a PFS of 7.5 months[223]. For patients with PARP-resistant ovarian cancer, the combination of olaparib and the WEE1 inhibitor adavosertib elicited improved clinical benefit (ORR 29%, DCR 89%) compared with adavosertib alone (ORR 23%, DCR 63%); however, in the BRCA-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR 19%) and monotherapy (ORR 20%) treatments[224].

Rucaparib

Assay findings association

Loss of Heterozygosity score
28.3%

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-3] . In platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma, the PARP inhibitor rucaparib elicited significantly longer median PFS and improved ORR for patients with LOH score ≥ 16%[1,3] .

SUPPORTING DATA

As first-line maintenance therapy evaluated in the Phase 3 ATHENA study, rucaparib monotherapy significantly improved median PFS (mPFS) compared with placebo for patients with ovarian cancer in both the homologous recombination deficient (HRD)-positive population (BRCA mutated or BRCA wildtype and high genomic loss of heterozygosity [LOH] score defined as ≥16%; mPFS of 28.7 vs. 11.3 months, HR=0.47) and the overall population (mPFS of 20.2 vs. 9.2 months, HR=0.52); exploratory subgroup analysis also reported benefit for the HRD-negative group (BRCA wildtype and low genomic LOH score defined as <16%; mPFS of 12.1 vs. 9.1 months, HR=0.65)[225]. In the Phase 3 ARIEL3 study of rucaparib maintenance treatment for patients with recurrent platinum-sensitive high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, mPFS was significantly improved with rucaparib compared with placebo for patients, irrespective of HRD or BRCA status, with benefit observed for both the LOH-high subgroup (13.6 vs. 5.4 months, HR=0.32) and the overall population (10.8 vs. 5.4 months, HR=0.36), with CR rates of 12% for the HRD-positive group and 7% for the overall population; PFS benefit was also observed for the BRCA-wildtype, LOH-low group (HR=0.58)[2]. In the Phase 2 ARIEL2 trial for patients with recurrent platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, mPFS on rucaparib was 5.7 months for patients with high LOH and 5.2 months for patients with low LOH[3].

Talazoparib

Assay findings association

Loss of Heterozygosity score
28.3%

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-3] . In platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma, the PARP inhibitor rucaparib elicited significantly longer median PFS and improved ORR for patients with LOH score ≥ 16%[1,3] .

SUPPORTING DATA

An ORR of 42% (5/12) was reported for patients with BRCA1/2-mutated ovarian cancer treated with talazoparib in a Phase 1 study[226]. In a Phase 2 study of talazoparib in advanced solid tumors, 1 patient with BRIP1-mutated ovarian carcinoma with wildtype BRCA status experienced a prolonged SD[227].

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.

BIOMARKER

Loss of Heterozygosity score

RATIONALE

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors.

RESULT

28.3%

NCT05489211

PHASE 2

Study of Dato-Dxd as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Tumours (TROPION-PanTumor03)

TARGETS
TROP2, PD-L1, PARP1, PD-1

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Liou Ying Township (Taiwan), Hangzhou (China), Shanghai (China), Zhengzhou (China), Seoul (Korea, Republic of), Chongqing (China), Suita-shi (Japan), Nagoya-shi (Japan)

NCT04434482

PHASE 1/2

IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer

TARGETS
PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Wuhan (China), Gyeonggi-do (Korea, Republic of), Seoul (Korea, Republic of), Cheongju-si (Korea, Republic of), Beijing (China), Jilin (China)

NCT05797168

PHASE 1/2

Phase I/IIa Study for AZD5335 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Solid Tumors

TARGETS
PARP1

LOCATIONS: Tainan City (Taiwan), Tokyo (Japan), Melbourne (Australia), Haifa (Israel), Ramat Gan (Israel), California, Texas

NCT04884360

PHASE 3

D9319C00001- 1L OC Mono Global RCT

TARGETS
PARP

LOCATIONS: Wenzhou (China), Jiaxing (China), Shanghai (China), Suzhou (China), Wuxi (China), Nanjing (China), Hefei (China), Beijing (China), Changchun (China), Changsha (China)

NCT04518501

PHASE 1/2

Fuzuloparib Arsenic Trioxide Platinum Resistance Relapsed Ovarian Cancer

TARGETS
RARA, PARP

LOCATIONS: Zhejiang (China)

NCT05489926

PHASE 2

A Study to Explore Pamiparib Treatment in Epithelial Ovarian Cancer After Prior PARP Inhibitor Exposure

TARGETS
PARP

LOCATIONS: Hangzhou (China)

NCT03983226

PHASE 2

Surgery and Niraparib in Secondary Recurrent Ovarian Cancer (SOC-3 Trial)

TARGETS
PARP

LOCATIONS: Shanghai (China)

NCT04586335

PHASE 1

Study of CYH33 in Combination With Olaparib an Oral PARP Inhibitor in Patients With Advanced Solid Tumors.

TARGETS
PARP, PI3K-alpha

LOCATIONS: Shanghai (China)

NCT03742895

PHASE 2

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

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Edirne (Turkey)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

GENE
TP53

ALTERATION
R196*

RATIONALE
TP53 loss of function alterations may predict sensitivity to WEE1 inhibitors.

NCT04516447

PHASE 1

A Study of ZN-c3 in Patients With Platinum-Resistant Ovarian Cancer

TARGETS
WEE1

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Nedlands (Australia), Sunshine Coast (Australia), South Brisbane (Australia), Melbourne (Australia), Belgrade (Serbia), Tuzla (Bosnia and Herzegovina), Banja Luka (Bosnia and Herzegovina), Colorado

NCT03968653

PHASE 1

Study of Oral Debio 0123 in Combination With Carboplatin in Participants With Advanced Solid Tumors

TARGETS
WEE1

LOCATIONS: Groningen (Netherlands), Nijmegen (Netherlands), Leiden (Netherlands), Barcelona (Spain)

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.

ARAF
NM_001654.3: c.1734G>C
(p.E578D)
chrX:47430769

AURKB
NM_004217.2: c.241C>T
(p.R81C)
chr17:8110651

BRD4
NM_014299.2: c.682G>A
(p.V228I)
chr19:15376332

CHEK1
amplification

EGFR
NM_005228.3: c.-38_26del
(p.M1?)
chr7:55086932-55086996

KDM5C
NM_004187.3: c.4094C>T
(p.P1365L)
chrX:53222978

KDM6A
NM_021140.2: c.1736G>A
(p.C579Y)
chrX:44922875

KMT2A (MLL)
NM_005933.3:
c.9742_9752del
(p.V3248Yfs*5)
chr11:118376357-118376368

KMT2D (MLL2)
NM_003482.4: c.12143C>T
(p.P4048L)
chr12:49426345

NTRK1
NM_002529.3: c.1697T>C
(p.M566T)
chr1:156846256

ORDERED TEST # ORD-1795940-01

APPENDIX Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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 PRINCIPLE

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® Sequencing platform (HiSeq 4000 or NovaSeq 6000), 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. 2023. 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 fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and

MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out 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%. HER2 overexpression occurs in 18-20% of breast cancers (Owens et al. 2004 [PMID: 15140287]; Salmon et al. 1987 [PMID: 3798106]; Yaziji et al. 2004 [PMID: 15113815]). Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

SOFTWARE VERSION INFORMATION

MR Suite Version (RG) 7.15.0
MR Reporting Config Version Config 49
Analysis Pipeline Version v3.29.0
Computational Biology Suite Version 6.29.0

The median exon coverage for this sample is 836x

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