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

PATIENT

DISEASE Ovary epithelial carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings

Loss of Heterozygosity score - 16.3 %
Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

NF1 loss exons 1-5
GATA6 amplification
TP53 V122fs*26

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

7 Therapies with Clinical Benefit
0 Therapies with Lack of Response
20 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Loss of Heterozygosity score - 16.3 %	Niraparib 2A	Talazoparib
10 Trials *see p. 10*	Olaparib 2A	
	Rucaparib 2A	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
***NF1* -** loss exons 1-5	none	Trametinib 2A
		Binimetinib
10 Trials *see p. 14*		Cobimetinib

NCCN category

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

GATA6 - amplification ..... p. 4 ***TP53*** - V122fs*26 ..... p. 5

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
16.3 %

POTENTIAL TREATMENT STRATEGIES

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

The loss of heterozygosity (LOH) score is a profile of the percentage of the tumor genome that is under focal loss of one allele[2]; focal LOH events accumulate as genomic "scars" as a result of incorrect DNA double-strand break repair when the homologous recombination pathway is deficient (HRD)[6,10,13-14]. HRD and consequent genomic LOH occur as a result of genetic or epigenetic inactivation of one or more of the homologous recombination pathway proteins, including BRCA1, BRCA2, RAD51C, ATM, PALB2, and BRIP1[13-16]. This sample harbors a genomic LOH score 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[2] and maintenance[1] settings.

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[17-19], including approved therapies nivolumab and pembrolizumab[20]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[21].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been reported in 1.6-19.7% of ovarian cancer samples[22-23], including 3.8% (1/26) of ovarian endometrioid adenocarcinomas[24], 10.0% (3/30) of ovarian clear cell carcinomas (CCOCs)[25] and 84.6% (11/13) of ovarian cystadenocarcinomas[26]. MSI-H was also frequently observed in ovarian cystadenomas (60.0%; 6/10) and normal ovary tissue (78.6%; 11/14)[26]. No association of MSI-H with stage or survival was found in patients with ovarian cancer[22,27].

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[28]. 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[28-30]. 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[31-33]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[28,30,32-33].

BIOMARKER

Tumor Mutational Burden

RESULT
4 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[34-36] and anti-PD-1 therapies[34-37]. Higher TMB has corresponded with increased ORR and OS from treatment with immune checkpoint inhibitors in pan-tumor studies[34-37]. Analyses across several solid tumor types have identified that patients with higher TMBs (≥16-20 Muts/Mb) achieved greater clinical benefit using PD-1/PD-L1 monotherapy, compared with patients treated with chemotherapy[38] or those with lower TMBs[35]. Additionally, higher TMB is significantly associated with improved OS with immune checkpoint inhibitor treatment for patients with advanced cancer across 9 solid tumor types[34]. However, the KEYNOTE 158 trial found significant improvement in ORR in a large cohort of patients with a TMB of ≥10 Muts/Mb compared with those with TMBs <10 across multiple solid tumor types, with similar findings observed in the KEYNOTE 028 and 012 trials[37]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1/PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Ovarian carcinomas, including peritoneal and Fallopian tube carcinomas, harbor a median TMB of 2.7-3.6 mutations per megabase (muts/Mb) depending upon subtype, and up to 2.1% of cases have high TMB (>20 muts/Mb)[39]. 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[40].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[41-42] and cigarette smoke in lung cancer[43-44], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[45-49], and microsatellite instability (MSI)[45,48-49]. 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[35-36].

GENE
NF1

ALTERATION
loss exons 1-5

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in neurofibromatosis type 1[50] and neurofibromatosis-associated glioma or glioblastoma[51-52] as well as extensive preclinical evidence in several tumor types[53-58], NF1 inactivation may predict sensitivity to MEK inhibitors, including the approved therapies cobimetinib, trametinib, and binimetinib. A Phase 2 trial of selumetinib reported a DCR of 96% (24/25) in pediatric patients with recurrent NF1-associated low-grade glioma, with 10 PRs and 14 SDs[51]. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including the approved agents everolimus and temsirolimus, based on limited clinical data[59-61] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[62-63]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[64]. 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[65], 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[66].

FREQUENCY & PROGNOSIS

In the Ovarian Serous Cystadenocarcinoma TCGA dataset, mutation and putative homozygous deletion of NF1 has been found in 3.8% and 7% of cases, respectively[15]. In the scientific literature, NF1 alterations have been found in 14-22% of ovarian carcinomas[67-68]. NF1 alterations have been reported to co-occur with TP53 mutations in ovarian serous carcinomas[68]. The prognostic significance of NF1 alteration in ovarian cancer is unclear (PubMed, Aug 2019). NF1 inactivation in ovarian cancer has been associated with resistance to platinum-based chemotherapy in clinical[69-70] and preclinical[71] studies.

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[72]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[73]. NF1 alterations that result in loss or disruption of the GAP-related domain[74-77], as observed here, are predicted to be inactivating[73,77-82]. Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[83-85]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[86-87], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
GATA6

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies available to address genomic alterations in GATA6.

FREQUENCY & PROGNOSIS

GATA6 was identified as a tumor suppressor in a preclinical model of astrocytoma and verified in human samples; GATA6 mutations, loss of GATA6 expression, or loss of heterozygosity were discovered in glioblastomas, but not in lower grade astrocytomas, and restoration of GATA6 inhibited glioblastoma cell line growth[88]. However, overexpression of GATA6 has been detected in pancreatic and bile duct carcinoma and is associated with increased proliferation, cell cycle progression, and colony formation, which have been shown to be inhibited by GATA6 siRNA knockdown in pancreatic carcinoma cell lines[89-90]. GATA6 overexpression in colorectal carcinoma is also associated with poor prognosis and metastasis[91].

FINDING SUMMARY

GATA6 encodes a zinc finger transcription factor, which is involved in the development of several tissues and is expressed in proliferating cells throughout the intestinal tract[92]. GATA6 has been described as both a tumor suppressor and an oncogene, which may be dependent on the tumor type.

GENE
TP53

ALTERATION
V122fs*26

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
365_366delTG

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[93-96], or p53 gene therapy and immunotherapeutics such as SGT-53[97-101] and ALT-801[102]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 10% (17/176) and SDs in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53 wild-type[103]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR in patients with platinum refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[104]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[105]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[106]. 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 in patients with TP53 alterations[107]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in 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[101]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutant, but not TP53-wild-type, breast cancer xenotransplant mouse model[108].

FREQUENCY & PROGNOSIS

TP53 alterations have been reported in 29-80% of ovarian tumors, with a higher incidence in high-grade pelvic (primary ovarian, tubal, or peritoneal) serous carcinoma, with incidence of 91-97%[15,109-115]. One study reports TP53 mutation in all subtypes of ovarian carcinoma, including 57% (8/14) of mucinous, 28% (8/29) of high grade endometrioid, and 52% (13/25) of clear cell cases[114]. One study reported TP53 mutation in 6.7% of low grade ovarian endometrioid carcinomas[116]. TP53 alterations have also been reported in serous tubal intraepithelial carcinomas (STICs) of the Fallopian tube, which are suggested to be precursor lesions of tubo-ovarian high grade serous carcinomas[117-120]. 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[114]. 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[121].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[122]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[123-125]. The TP53 variant observed here has been described in the ClinVar database as a pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with Li-Fraumeni syndrome (ClinVar, Nov 2019)[126]. 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[127-129], including sarcomas[130-131]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[132] to 1:20,000[131]. 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[133]. In the appropriate clinical context, germline testing of TP53 is recommended.

Niraparib

Assay findings association

Loss of Heterozygosity score
16.3 %

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,134] . 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%[2,134] .

SUPPORTING DATA

In the maintenance setting for patients with ovarian, Fallopian tube, or primary peritoneal cancer, Phase 3 studies have shown niraparib to significantly increase median PFS (mPFS) relative to placebo[3,135] . The Phase 3 PRIMA trial reported significantly extended mPFS from niraparib maintenance therapy after response to first-line platinum chemotherapy for patients with newly-diagnosed ovarian cancer and homologous recombination-deficient (HRD) tumors (21.9 vs. 10.4 months; HR=0.43) and for the overall population (13.8 vs. 8.2 months; HR=0.62). For patients with HRD tumors, benefit was irrespective of BRCA status (BRCA-mutated, HR=0.40; BRCA wild-type, HR=0.50); patients with HR-proficient tumors also experienced PFS benefit (HR=0.68, p=0.02)[135]. The Phase 3 ENGOT-OV16/NOVA study showed niraparib maintenance therapy to significantly increase mPFS, compared to placebo, for patients with platinum-sensitive recurrent ovarian cancer and germline BRCA (gBRCA) mutations (21.0 vs. 5.5 months) and without gBRCA mutations (9.3 vs. 3.9 months), as well as for a patient subgroup without gBRCA mutations with HRD tumors (12.9 vs. 3.8 months)[3]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40.0% (8/20) of patients with ovarian cancer and BRCA mutations experienced a PR[136]. In the Phase 1/2 TOPACIO/KEYNOTE-162 study of niraparib in combination with pembrolizumab in patients with platinum-resistant ovarian cancer, the ORR was 18.3%, the DCR was 65.0% (3 CRs, 8 PRs, 28 SDs, 20 PDs), and mPFS was 3.4 months; no significant differences in efficacy were noted among analyzed subgroups (ORRs of 18.2% for patients with BRCA mutations vs. 19.1% for patients with BRCA wild-type tumors; 14.3% for patients with HRD-positive vs. 18.8 for patients with HRD-negative tumors; and 21.2% for patients with PD-L1-positive tumors vs. 9.5 for patients with PD-L1-negative tumors)[137]. A Phase 1 study of the combination of niraparib and bevacizumab for patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 90.9% (10/11), with a response rate of 45.5% (5/11)[138]. The follow-up Phase 2 trial comparing niraparib plus bevacizumab to niraparib alone found significant improvement in PFS with addition of bevacizumab (mPFS of 11.9 months for niraparib plus bevacizumab vs. 5.5 months for niraparib; HR=0.35; p<0.0001)[139].

Olaparib

Assay findings association

Loss of Heterozygosity score
16.3 %

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, with or without deleterious or suspected deleterious somatic or germline BRCA (gBRCA) mutations, as well as deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,134] . 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%[2,134] .

SUPPORTING DATA

Olaparib has been studied primarily for the treatment of ovarian cancer, particularly for 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[140-141] , and for patients with cancer classified as platinum-sensitive versus platinum-resistant[141-144] . As a maintenance therapy for patients with newly diagnosed or platinum-sensitive relapsed ovarian cancer, olaparib monotherapy has demonstrated significantly improved median PFS and OS compared to placebo in the Phase 3 SOLO-1 study[145] and multiple later-phase studies[146-149] . In a retrospective analysis of the SOLO-1 study, similar benefit of olaparib over placebo was observed for patients with genomic LOH scores ≥16 (HR=0.29) compared to those with LOH scores <16 (HR=0.29)[150]. Statistically superior median PFS from treatment with olaparib in combination with the VEGF-inhibitor bevacizumab as compared to 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 (PFS: 22.1 vs. 16.6 months), the BRCA1/2-mutated population (PFS: 37.2 vs. 21.7 months), and in the BRCA1/2-wild-type population harboring HRD-positive status (PFS: 28.1 vs. 16.6 months)[151]. For patients with platinum-sensitive recurrent ovarian cancer who previously progressed on chemotherapy, statistically increased median PFS was reported in a Phase 2 study of olaparib in combination with chemotherapy (PFS: 12.2 months) as compared to chemotherapy alone (PFS: 9.6 months)[152], as well as from treatment with the VEGFR-inhibitor cediranib as compared with olaparib monotherapy in a Phase 1/2 trial[153].

Rucaparib

Assay findings association

Loss of Heterozygosity score
16.3 %

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,134] . 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%[2,134] .

SUPPORTING DATA

In a Phase 3 study of rucaparib maintenance treatment for patients with platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or Fallopian tube carcinoma in response to platinum therapy, median PFS was significantly improved with rucaparib compared to placebo for patients with germline or somatic BRCA mutations (16.6 vs. 5.4 months, HR=0.23), patients with BRCA-mutated or BRCA wild-type and high loss of heterozygosity (LOH) tumors (collectively homologous recombination-deficient [HRD] tumors) (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 18% (BRCA-mutated), 12% (HRD) and 7% (overall), and PFS benefit observed in the BRCA-wild-type and LOH-low group (HR=0.58)[1]. In a Phase 2 trial for patients with recurrent, platinum-sensitive ovarian, peritoneal, or Fallopian tube carcinoma, median PFS on rucaparib was significantly longer for patients with BRCA1/2 mutations (12.8 months) or high LOH (5.7 months) compared with patients with low LOH (5.2 months)[2]. Patients with high-grade ovarian carcinoma and deleterious BRCA mutations who had previously been treated with at least 2 chemotherapies achieved an ORR of 54% (9% CR, 45% PR) and a median duration of response of 9.2 months[2,154-155] . In a separate Phase 2 study of rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92.3% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously[156].

Binimetinib

Assay findings association

NF1
loss exons 1-5

AREAS OF THERAPEUTIC USE

Binimetinib is a MEK inhibitor that is FDA approved in combination with encorafenib to treat patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

GENE ASSOCIATION

On the basis of clinical evidence[50,52] and strong preclinical evidence[53-58] , NF1 inactivation may predict sensitivity to MEK inhibitors such as binimetinib.

SUPPORTING DATA

The Phase 3 MILO study of binimetinib versus physician's choice chemotherapy for patients with low-grade serous ovarian carcinoma reported no significant improvement in median PFS (9.1 months versus 10.6 months) and did not meet its primary end point[157]. A Phase 1b study evaluating the combination of binimetinib and paclitaxel in patients with platinum-resistant epithelial ovarian cancer reported an ORR of 17.9% (5/28) and a DCR of 57.1% (16/28)[158]. Clinical benefit, including a CR in a patient harboring a BRAF fusion, was reported in all 4 patients with MAPK pathway mutations[158]. PRs were reported in 2 patients with KRAS-mutant ovarian cancer treated with single-agent binimetinib[159].

Cobimetinib

Assay findings association

NF1
loss exons 1-5

AREAS OF THERAPEUTIC USE

Cobimetinib is a MEK inhibitor that is FDA approved in combination with vemurafenib for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

GENE ASSOCIATION

On the basis of clinical evidence[50,52] and strong preclinical evidence[54-58] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

In a Phase 1b study, out of 47 patients treated with cobimetinib and the AKT inhibitor ipatasertib, 3 patients with KRAS-mutant ovarian, mesonephric cervical, or endometrial carcinoma had PR, with prolonged SD lasting for >6 months[160]. Other clinical trials of combination treatment with MEK and PI3K inhibitors have also reported clinical responses for patients with KRAS-mutated ovarian cancer[106,161-162] .

Talazoparib

Assay findings association

Loss of Heterozygosity score
16.3 %

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.

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,134] . 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%[2,134] .

SUPPORTING DATA

An ORR of 42% (5/12) was reported in patients with BRCA-mutated ovarian cancer treated with talazoparib in a Phase 1 study[163]. In a Phase 2 study of talazoparib in advanced solid tumors, 1 patient with BRIP1-mutated ovarian carcinoma lacking BRCA1/2 alterations experienced a prolonged SD[164].

Trametinib

Assay findings association

NF1
loss exons 1-5

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy and in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as well as in combination with dabrafenib as adjuvant treatment for completely resected advanced BRAF V600E- or V600K-positive melanoma. It is also approved in combination with dabrafenib to treat patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation and to treat patients with BRAF V600E-positive anaplastic thyroid cancer (ATC) who lack satisfactory locoregional treatment options.

GENE ASSOCIATION

On the basis of clinical evidence[50,52] and strong preclinical evidence[54-58] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

A randomized Phase 2/3 study reported improved median PFS (13.0 months vs. 7.2 months, [HR=0.48]), ORR (26.2% vs. 6.2%) and OS (37.0 months vs. 29.2 months) for patients with recurrent or progressive low-grade serous ovarian carcinoma (LGSC) treated with trametinib compared to physician's choice standard of care[165]. A Phase 2 study of the MEK inhibitor selumetinib in patients with recurrent LGSC reported a response rate of 15.4% (8/52, including 1 CR and 7 PRs) and SD of 65.0%; in an exploratory analysis of 32 samples, KRAS or NRAS mutation status was not significantly correlated with response[166]. A case study described significant and prolonged response to trametinib monotherapy in a patient with KRAS-mutant LGSC[167]. A patient with NRAS-mutant, recurrent LGSC experienced a rapid response to trametinib treatment[168]. A clinical trial of combination treatment with trametinib and the PI3K inhibitor buparlisib observed a 28.6% response rate (6/21) in patients with ovarian cancer; in this study 19/21 patients harbored a KRAS mutation[169]. Other clinical trials of combination treatment with MEK and PI3K inhibitors have also reported clinical responses for patients with KRAS-mutated ovarian cancer[106,161-162] . 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[65], 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[66].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient's tumor type.

CLINICAL TRIALS

IMPORTANT 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

RESULT

16.3 %

RATIONALE

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

NCT03709316

PHASE 3

A Study of ZL-2306 (Niraparib) as Maintenance Treatment Following First-line Chemotherapy in Patients With Advanced Ovarian Cancer

TARGETS
PARP

LOCATIONS: Hefei (China), Fuzhou (China), Guangzhou (China), Guiyang (China), Harbin (China), Zhengzhou (China), Wuhan (China), Changsha (China), Nanjing (China), Changchun (China), Shenyang (China), Xi'an (China), Jinan (China), Taiyuan (China), Chengdu (China), Urumqi (China), Kunming (China), Hangzhou (China), Wenzhou (China), Beijing (China), Chongqing (China), Shanghai (China), Tianjin (China)

NCT03705156

PHASE 3

Clinical Trial Evaluating the Efficacy and Safety of ZL-2306 (Niraparib) in Ovarian Cancer Patient

TARGETS
PARP

LOCATIONS: Guangzhou (China), Harbin (China), Wuhan (China), Changsha (China), Nanjing (China), Changchun (China), Shenyang (China), Xi'an (China), Jinan (China), Chengdu (China), Urumqi (China), Hangzhou (China), Beijing (China), Chongqing (China), Shanghai (China), Tianjin (China)

NCT03330405

PHASE 2

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

TARGETS
PD-L1, PARP

LOCATIONS: Edmonton (Canada), Arkansas, California, District of Columbia, Obninsk (Russian Federation), Massachusetts, Minnesota, Sydney (Australia), New York, Ohio, Toronto (Canada), Brisbane (Australia), Texas, Murdoch (Australia), Brussels (Belgium), Bruxelles (Belgium), Charleroi (Belgium), Copenhagen (Denmark), Herlev (Denmark), Budapest (Hungary), Miskolc (Hungary), Pecs (Hungary), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Moscow (Russian Federation), Omsk (Russian Federation), Yaroslavl (Russian Federation), Leicester (United Kingdom), London (United Kingdom), Newcastle Upon Tyne (United Kingdom)

CLINICAL TRIALS

NCT03522246

PHASE 3

A Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy

TARGETS
PARP, PD-1

LOCATIONS: Albury (Australia), Calgary (Canada), Edmonton (Canada), Arizona, Chaidari (Greece), Abbotsford (Canada), Kelowna (Canada), Surrey (Canada), California, Kashiwa (Japan), Cluj-Napoca (Romania), Colorado, Connecticut, Florida, Georgia, Goyang-si (Korea, Republic of), Seongnam (Korea, Republic of), Seongnam-si (Korea, Republic of), Southampton (United Kingdom), Illinois, Indiana, Iowa, Oradea (Romania), Kawasaki-shi (Japan), Kansas, Canterbury (United Kingdom), Kentucky, Tooting (United Kingdom), Louisiana, Maine, Winnipeg (Canada), Maryland, Massachusetts, Michigan, Northwood (United Kingdom), Minnesota, Missouri, Nevada, New Jersey, New Lambton Heights (Australia), Saint Leonards (Australia), Sydney (Australia), Westmead (Australia), New York, North Carolina, Cliftonville (United Kingdom), Halifax (Canada), Ohio, Oklahoma, Hamilton (Canada), London (Canada), Toronto (Canada), Oregon, Pennsylvania, Montréal (Canada), Sherbrooke (Canada), Brisbane (Australia), Hidaka (Japan), Incheon (Korea, Republic of), Toorak Gardens (Australia), South Dakota, Texas, Utah, Melbourne (Australia), Virginia, Subiaco (Australia), Bebington (United Kingdom), Wisconsin, Leuven (Belgium), Aalborg (Denmark), Odense (Denmark), Kuopio (Finland), Athens (Greece), Patra (Greece), Thessaloniki (Greece), Cork (Ireland), Dublin (Ireland), Limerick (Ireland), Waterford (Ireland), Hadera (Israel), Kfar Saba (Israel), Nahariya (Israel), Ramat Gan (Israel), Safed (Israel), Tel Aviv (Israel), Aviano (Italy), Candiolo (Italy), Catania (Italy), Catanzaro (Italy), Napoli (Italy), Reggio Emilia (Italy), Roma (Italy), Vicenza (Italy), Tokyo (Japan), Seoul (Korea, Republic of), Auckland (New Zealand), Christchurch (New Zealand), Hamilton (New Zealand), Palmerston North (New Zealand), Tauranga (New Zealand), Bialystok (Poland), Białystok (Poland), Gdynia (Poland), Kielce (Poland), Lublin (Poland), Poznań (Poland), Szczecin (Poland), Warszawa (Poland), Braşov (Romania), Bucharest (Romania), Craiova (Romania), Iaşi (Romania), Suceava (Romania), Timişoara (Romania), Arkhangel'sk (Russian Federation), Kursk (Russian Federation), Omsk (Russian Federation), Pesochnyy (Russian Federation), Pyatigorsk (Russian Federation), Saint Petersburg (Russian Federation), Saransk (Russian Federation), Singapore (Singapore), Barcelona (Spain), Bilbao (Spain), Castillón (Spain), El Palmar (Spain), Jerez de la Frontera (Spain), Madrid (Spain), Oviedo (Spain), Palma De Mallorca (Spain), Santander (Spain), Sevilla (Spain), Kaohsiung (Taiwan), New Taipei City (Taiwan), Taichung (Taiwan), Taipei (Taiwan), Taoyuan (Taiwan), Ankara (Turkey), Manisa (Turkey), Birmingham (United Kingdom), Brighton (United Kingdom), Bristol (United Kingdom), Cambridge (United Kingdom), Dundee (United Kingdom), Edinburgh (United Kingdom), Lancaster (United Kingdom), Leeds (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom), Poole (United Kingdom), Preston (United Kingdom), Sutton (United Kingdom), Swansea (United Kingdom), Taunton (United Kingdom)

NCT03740165

PHASE 3

Study of Chemotherapy With Pembrolizumab (MK-3475) Followed by Maintenance With Olaparib (MK-7339) for the First-Line Treatment of Women With BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (MK-7339-001/ENGOT-ov43/KEYLYNK-001)

TARGETS
PARP, PD-1

LOCATIONS: Calgary (Canada), Fortaleza (Brazil), Kashiwa (Japan), Bogota (Colombia), Port Elizabeth (South Africa), Matsuyama (Japan), Toon (Japan), Florida, Parktown-Johannesburg (South Africa), Pretoria (South Africa), Ota (Japan), Seongnam-si (Korea, Republic of), Sapporo (Japan), Shiwa-gun (Japan), Kawasaki (Japan), Nebraska, Kogarah (Australia), Ohio, Nakagami-gun (Japan), Kingston (Canada), Mississauga (Canada), Toronto (Canada), Chicoutimi (Canada), Montreal (Canada), Cairns (Australia), Rio de Janeiro (Brazil), Ijui (Brazil), Lajeado (Brazil), Porto Alegre (Brazil), Rhode Island, Sao Paulo (Brazil), Hidaka (Japan), Kitaadachi-gun (Japan), Tokorozawa (Japan), Gliwice (Poland), Kielce (Poland), Torino (Italy), Mitaka (Japan), Cali (Colombia), Vina del Mar (Chile), Clayton (Australia), St Albans (Australia), Cape Town (South Africa), George (South Africa), Kraaifontein (South Africa), Ballarat (Australia), Brussels (Belgium), Charleroi (Belgium), Gent (Belgium), Hasselt (Belgium), Leuven (Belgium), Libramont (Belgium), Liege (Belgium), Goiania (Brazil), Antofagasta (Chile), Santiago (Chile), Temuco (Chile), Barranquilla (Colombia), Monteria (Colombia), Valledupar (Colombia), Brno (Czechia), Olomouc (Czechia), Ostrava-Poruba (Czechia), Praha (Czechia), Lyon (France), Nancy (France), Nimes (France), Paris (France), Saint-Priest-en-Jarez (France), Strasbourg (France), Villejuif (France), Budapest (Hungary), Debrecen (Hungary), Miskolc (Hungary), Pecs (Hungary), Beer-Sheva (Israel), Hadera (Israel), Haifa (Israel), Holon (Israel), Jerusalem (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Bari (Italy), Benevento (Italy), Catania (Italy), Lecco (Italy), Milano (Italy), Napoli (Italy), Padova (Italy), Roma (Italy), Trento (Italy), Udine (Italy), Kagoshima (Japan), Niigata (Japan), Osaka (Japan), Tokyo (Japan), Seoul (Korea, Republic of), Bialystok (Poland), Gdynia (Poland), Poznan (Poland), Warszawa (Poland), Arkhangelsk (Russian Federation), Kazan (Russian Federation), Moscow (Russian Federation), Obninsk (Russian Federation), Saint Petersburg (Russian Federation), St. Petersburg (Russian Federation), Ufa (Russian Federation), Durban (South Africa), Johannesburg (South Africa), A Coruna (Spain), Caceres (Spain), Hospitalet de Llobregat (Spain), Lugo (Spain), Madrid (Spain), Manresa (Spain), San Sebastian (Spain), Sevilla (Spain), Terrassa (Spain), Valencia (Spain), Changhua (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Taoyuan (Taiwan), Ankara (Turkey), Antalya (Turkey), Bursa (Turkey), Istanbul (Turkey), Kucukcekmece (Turkey), Sakarya (Turkey), Ivano-Frankivsk (Ukraine), Kharkiv (Ukraine), Khmelnitskiy (Ukraine), Kyiv (Ukraine), Lviv (Ukraine), Odesa (Ukraine), Sumy (Ukraine), Uzhgorod (Ukraine)

NCT03602859

PHASE 3

A Phase 3 Comparison of Platinum-Based Therapy With TSR-042 and Niraparib Versus Standard of Care Platinum-Based Therapy as First-Line Treatment of Stage III or IV Nonmucinous Epithelial Ovarian Cancer

TARGETS
PD-1, PARP

LOCATIONS: Alaska, Edmonton (Canada), Brasschaat (Belgium), Bordeaux (France), Berlin (Germany), Neumarkt (Germany), Plerin (France), Vancouver (Canada), California, Cluj-Napoca (Romania), Connecticut, Craiova (Romania), Leuven (Belgium), Florida, Hamburg (Germany), Paris (France), Illinois, Montpellier (France), Louisiana, San Sebastián (Spain), Maine, Maryland, Massachusetts, Minnesota, Montana, Wolfsburg (Germany), New Jersey, New York, North Carolina, Ohio, Oklahoma, Hamilton (Canada), London (Canada), Toronto (Canada), Oregon, Cholet Cedex (France), Pennsylvania, Avignon Cedex 9 (France), Montréal (Canada), Sherbrooke (Canada), Rhode Island, Lyon (France), South Dakota, Tennessee, Texas, Utah, Virginia, Washington, Minsk (Belarus), Brussels (Belgium), Praha (Czechia), Praha 8 - Liben (Czechia), Copenhagen (Denmark), Herlev (Denmark), Roskilde (Denmark), Helsinki (Finland), Kuopio (Finland), Tampere (Finland), Turku (Finland), Besancon (France), Caen (France), Clermont-Ferrand (France), Dijon (France), Grenoble (France), La Roche-sur-Yon (France), Le Mans (France), Lille (France), Marseille (France), Mont-de-Marsan (France), Nancy (France), Nantes (France), Nice Cedex 2 (France), Nîmes (France), Paris Cedex 05 (France), Pierre-Bénite (France), Poitiers (France), Reims (France), Saint Priest en Jarez (France), Strasbourg (France), Toulouse Cedex 9 (France), Tours (France), Ravensburg (Germany), Be'er Sheva (Israel), Haifa (Israel), H?olon (Israel), Petach Tikva (Israel), Re?ovot (Israel), Bucuresti (Romania), Constanța (Romania), Timisoara (Romania), Barcelona (Spain), Girona (Spain), Jaen (Spain), Madrid (Spain), Santiago De Compostela (Spain), Toledo (Spain), Valencia (Spain), Zaragoza (Spain), Ávila (Spain), Chernihiv (Ukraine), Lviv (Ukraine), Glasgow (United Kingdom), Portsmouth (United Kingdom), Truro (United Kingdom)

NCT03737643

PHASE 3

Durvalumab Treatment in Combination With Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib Treatment in Advanced Ovarian Cancer Patients.

TARGETS
VEGFA, PD-L1, PARP

LOCATIONS: California, Florida, Georgia, Illinois, Indiana, Maryland, Michigan, Missouri, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Barrie (Canada), Sudbury (Canada), Toronto (Canada), Pennsylvania, Montreal (Canada), Rimouski (Canada), Utah, Graz (Austria), Innsbruck (Austria), Linz (Austria), Wien (Austria), Aalst (Belgium), Leuven (Belgium), Namur (Belgium), Oostende (Belgium), Sint-Niklaas (Belgium), Plovdiv (Bulgaria), Sofia (Bulgaria), Varna (Bulgaria), Quebec (Canada), Aalborg (Denmark), Aarhus N (Denmark), Odense C (Denmark), Roskilde (Denmark), Vejle (Denmark), Kuopio (Finland), Oulu (Finland), Turku (Finland), Besançon (France), Bordeaux (France), Marseille (France), Paris (France), Paris Cedex 14 (France), Saint Herblain Cedex (France), Vandoeuvre les Nancy (France), Bad Homburg v.d.H. (Germany), Berlin (Germany), Bielefeld (Germany), Brandenburg (Germany), Dresden (Germany), Düsseldorf (Germany), Essen (Germany), Esslingen am Neckar (Germany), Frankfurt (Germany), Greifswald (Germany), Gütersloh (Germany), Hamburg (Germany), Hannover (Germany), Jena (Germany), Karlsruhe (Germany), Kassel (Germany), Kiel (Germany), Köln (Germany), Leipzig (Germany), Ludwigsburg (Germany), Lübeck (Germany), Mainz (Germany), München (Germany), Offenbach am Main (Germany), Rosenheim (Germany), Rostock (Germany), Saalfeld (Germany), Schweinfurt (Germany), Tübingen (Germany), Ulm (Germany), Worms (Germany), Budapest (Hungary), Debrecen (Hungary), Györ (Hungary), Kaposvár (Hungary), Szeged (Hungary), Zalaegerszeg (Hungary), Brescia (Italy), Lecce (Italy), Milano (Italy), Mirano (Italy), Naples (Italy), Reggio Calabria (Italy), Roma (Italy), Fukuoka-shi (Japan), Kashiwa-shi (Japan), Kobe-shi (Japan), Koto-ku (Japan), Kurume-shi (Japan), Kyoto-shi (Japan), Minato-ku (Japan), Nagoya-shi (Japan), Niigata-shi (Japan), Sapporo-shi (Japan), Sendai-shi (Japan), Shinjuku-ku (Japan), Sunto-gun (Japan), Toyoake-shi (Japan), Goyang-si (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Suwon-si (Korea, Republic of), Gdynia (Poland), Poznan (Poland), Szczecin (Poland), Warszawa (Poland), Łódź (Poland), Córdoba (Spain), Madrid (Spain), Terrassa(Barcelona) (Spain), Vigo (Spain), Adana (Turkey), Ankara (Turkey), Istanbul (Turkey), Izmir (Turkey)

NCT03106987

PHASE 3

A Study to Examine Olaparib Maintenance Retreatment in Patients With Epithelial Ovarian Cancer.

TARGETS
PARP

LOCATIONS: London (Canada), Montreal (Canada), Leuven (Belgium), Liège (Belgium), Namur (Belgium), Toronto (Canada), Aalborg (Denmark), København Ø (Denmark), Odense C (Denmark), Besançon (France), Bordeaux (France), Caen Cedex 05 (France), Clermont Ferrand cedex 01 (France), Lille (France), Lyon (France), Marseille (France), Montpellier (France), Nantes (France), Nice (France), Paris (France), Paris Cedex 20 (France), Paris Cedex 5 (France), Pierre Benite (France), Plerin SUR MER (France), Saint Herblain (France), Saint-cloud (France), Toulouse Cedex 09 (France), Vandoeuvre-Les-Nancy (France), Berlin (Germany), Dresden (Germany), Essen (Germany), Frankfurt (Germany), Greifswald (Germany), Halle (Germany), Hamburg (Germany), Hannover (Germany), Heidelberg (Germany), Jena (Germany), Köln (Germany), Lübeck (Germany), München (Germany), Regensburg (Germany), Rostock (Germany), Stuttgart (Germany), Ulm (Germany), Wiesbaden (Germany), Haifa (Israel), Holon (Israel), Jerusalem (Israel), Kfar Saba (Israel), Ramat Gan (Israel), Tel-Aviv (Israel), petach Tikva (Israel), Bologna (Italy), Brescia (Italy), Candiolo (Italy), Catania (Italy), Lecce (Italy), Milano (Italy), Modena (Italy), Napoli (Italy), Pisa (Italy), Reggio Emilia (Italy), Roma (Italy), Torino (Italy), Oslo (Norway), Grzepnica (Poland), Krakow (Poland), Lublin (Poland), Olsztyn (Poland), Poznań (Poland), Warszawa (Poland), A Coruña (Spain), Barcelona (Spain), Córdoba (Spain), L'Hospitalet de Llobregat (Spain), Madrid (Spain), Malaga (Spain), Sevilla (Spain), Valencia (Spain), Dundee (United Kingdom), Glasgow (United Kingdom), Leeds (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Taunton (United Kingdom), Wirral (United Kingdom)

CLINICAL TRIALS

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: Nagoya (Japan), Medellin (Colombia), Arizona, Oradea (Romania), Berazategui (Argentina), Ciudad de Buenos Aires (Argentina), California, Chelyabinsk (Russian Federation), Kashiwa (Japan), Comuna Floresti (Romania), Bogota (Colombia), Craiova (Romania), Georgia, Seongnam-si (Korea, Republic of), Guadalajara (Mexico), Istanbul (Turkey), Kentucky, Trujillo (Peru), Pozuelo de Alarcon (Spain), Maryland, Massachusetts, Michigan, Nebraska, New Jersey, Port Macquarie (Australia), New York, Monterrey (Mexico), Oklahoma, Suita (Japan), Pennsylvania, Montreal (Canada), South Dakota, Darlinghurst (Australia), Madero (Mexico), Utah, Washington, Nedlands (Australia), Buenos Aires (Argentina), Quebec (Canada), Barranquilla (Colombia), Cali (Colombia), Monteria (Colombia), Valledupar (Colombia), Copenhagen (Denmark), Herlev (Denmark), Odense (Denmark), Bordeaux (France), Dijon (France), Nice (France), Poitiers (France), Strasbourg (France), Villejuif (France), Guatemala (Guatemala), Quetzaltenango (Guatemala), Cork (Ireland), Dublin (Ireland), Haifa (Israel), Jerusalem (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Napoli (Italy), Rozzano (Italy), Siena (Italy), Kyoto (Japan), Tokyo (Japan), Seoul (Korea, Republic of), Chihuahua (Mexico), Mexico City (Mexico), Oaxaca (Mexico), Santiago De Quetaro (Mexico), Lima (Peru), Brasov (Romania), Bucuresti (Romania), Cluj Napoca (Romania), Arkhangelsk (Russian Federation), Kazan (Russian Federation), Moscow (Russian Federation), Ryazan (Russian Federation), Saint Petersburg (Russian Federation), Saint-Petersburg (Russian Federation), Samara (Russian Federation), St.Petersburg (Russian Federation), Barcelona (Spain), Bellinzona (Switzerland), Geneva (Switzerland), Zuerich (Switzerland), Adana (Turkey), Ankara (Turkey), Antalya (Turkey), Edirne (Turkey), Izmir (Turkey), Konya (Turkey), Manchester (United Kingdom), Newcastle-upon-Tyne (United Kingdom), Oxford (United Kingdom), Sheffield (United Kingdom)

NCT02921919

PHASE 2

Open-Label Extension and Safety Study of Talazoparib

TARGETS
PARP

LOCATIONS: California, Florida, Indiana, Massachusetts, Michigan, Hamilton (Canada), Montreal (Canada), Sutton (United Kingdom), Texas, Marseille cedex 09 (France), Erlangen (Germany), Budapest (Hungary), Warszawa (Poland), Moscow (Russian Federation), Saint-Petersburg (Russian Federation)

CLINICAL TRIALS

GENE
NF1

ALTERATION
loss exons 1-5

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

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)

NCT01827384

PHASE 2

Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, mTOR, MEK, WEE1

LOCATIONS: Colorado, Georgia, Kentucky, Maryland, Missouri, New Jersey, Pennsylvania, Texas

NCT03363867

PHASE 2

BEACON - Targeting the C1 Subtype of High Grade Serous Ovarian Cancer

TARGETS
MEK, PD-L1, VEGFA

LOCATIONS: Melbourne (Australia)

NCT03695380

PHASE 1

A Clinical Study of Cobimetinib Administered in Combination With Niraparib, With or Without Atezolizumab to Patients With Advanced Platinum-sensitive Ovarian Cancer

TARGETS
PARP, PD-L1, MEK

LOCATIONS: Arizona, California, Napoli (Italy), Florida, Georgia, A Coruna (Spain), Rome (Italy), Milano (Italy), Maryland, Missouri, New York, Oklahoma, Tennessee, Wisconsin, Girona (Spain), Jaen (Spain), Madrid (Spain), Valencia (Spain)

NCT03648489

PHASE 2

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

TARGETS
mTORC1, mTORC2

LOCATIONS: Barrow In Furness (United Kingdom), London (United Kingdom), London Borough of Sutton (United Kingdom), Manchester (United Kingdom), Lancaster (United Kingdom), Northwood (United Kingdom), Nottingham (United Kingdom), Oxford (United Kingdom), Southampton (United Kingdom)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Blacktown (Australia), Randwick (Australia), Melbourne (Australia), Nedlands (Australia)

CLINICAL TRIALS

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03833427

PHASE 1

Study of Selumetinib (MK-5618) in Combination With Pembrolizumab (MK-3475) in Participants With Advanced/Metastatic Solid Tumors (MK-5618-001)

TARGETS
PD-1, MEK

LOCATIONS: California, Michigan, New Jersey, Toronto (Canada), Texas, Quebec (Canada)

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Vancouver (Canada), California, Florida, Missouri, Toronto (Canada), Texas

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, Massachusetts, New Jersey, New York

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.

BTG1 R7W	***ERBB2*** R1230W	***ERCC4*** *917Rext*84	***JAK1*** A1049T
MAP2K2 (MEK2) loss	***MPL*** T601I	***NOTCH2*** Y1186C	***PBRM1*** G765R

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)

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 Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NCCN Categorization

Biomarker and genomic findings detected may be associated with certain National Comprehensive Cancer Network (NCCN) Compendium drugs or biologics (www.nccn.org). The NCCN categories 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.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is defined based on counting the total number of all synonymous and nonsynonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
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.

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

PDF Service version: 2.6.0

The median exon coverage for this sample is 916x

1. Coleman RL, Oza AM, Lorusso D, et al. ePub Oct 2017 (2017) PMID: 28916367
2. Swisher EM, Lin KK, Oza AM, et al. ePub Jan 2017 (2017) PMID: 27908594
3. Mirza MR, Monk BJ, Herrstedt J, et al. ePub 12 2016 (2016) PMID: 27717299
4. Telli ML, Timms KM, Reid J, et al. 22 (15):3764-73 (2016) PMID: 26957554
5. Timms KM, Abkevich V, Hughes E, et al. ePub Dec 2014 (2014) PMID: 25475740
6. Wang ZC, Birkbak NJ, Culhane AC, et al. 18 (20):5806-15 (2012) PMID: 22912389
7. Telli ML, Jensen KC, Vinayak S, et al. ePub Jun 2015 (2015) PMID: 25847929
8. Isakoff SJ, Mayer EL, He L, et al. ePub Jun 2015 (2015) PMID: 25847936
9. Elvin et al., 2017; ASCO Abstract 5512
10. Abkevich V, Timms KM, Hennessy BT, et al. ePub Nov 2012 (2012) PMID: 23047548
11. Marquard AM, Eklund AC, Joshi T, et al. 3 :9 (2015) PMID: 26015868
12. Pedersen BS, Konstantinopoulos PA, Spillman MA, et al. ePub Sep 2013 (2013) PMID: 23716468
13. Watkins JA, Irshad S, Grigoriadis A, et al. ePub Jun 2014 (2014) PMID: 25093514
14. Vanderstichele A, Busschaert P, Olbrecht S, et al. ePub 11 2017 (2017) PMID: 28950147
15. null ePub Jun 2011 (2011) PMID: 21720365
16. null ePub May 2003 (2003) PMID: 12736286
17. Gatalica Z, Snyder C, Maney T, et al. ePub Dec 2014 (2014) PMID: 25392179
18. Kroemer G, Galluzzi L, Zitvogel L, et al. 4 (7):e1058597 (2015) PMID: 26140250
19. Lal N, Beggs AD, Willcox BE, et al. 4 (3):e976052 (2015) PMID: 25949894
20. Le DT, Uram JN, Wang H, et al. ePub Jun 2015 (2015) PMID: 26028255
21. Ayers et al., 2016; ASCO-SITC Abstract P60
22. Segev Y, Zhang S, Akbari MR, et al. 36 (6):681-4 (2015) PMID: 26775351
23. Plisiecka-Hałasa J, Dansonka-Mieszkowska A, Kraszewska E, et al. 28 (2A):989-96 (null) PMID: 18507046
24. Huang HN, Lin MC, Tseng LH, et al. ePub Mar 2015 (2015) PMID: 25195947
25. Strickland et al., 2016; ASCO Abstract 5514
26. Caliman LP, Tavares RL, Piedade JB, et al. 4 (3):556-560 (2012) PMID: 22970055
27. Aysal A, Karnezis A, Medhi I, et al. ePub Feb 2012 (2012) PMID: 22189970
28. Kocarnik JM, Shiovitz S, Phipps AI 3 (4):269-76 (2015) PMID: 26337942
29. You JF, Buhard O, Ligtenberg MJ, et al. ePub Dec 2010 (2010) PMID: 21081928
30. Bairwa NK, Saha A, Gochhait S, et al. ePub 2014 (2014) PMID: 24623249
31. Boland CR, Thibodeau SN, Hamilton SR, et al. 58 (22):5248-57 (1998) PMID: 9823339
32. Pawlik TM, Raut CP, Rodriguez-Bigas MA 20 (4-5):199-206 (2004) PMID: 15528785
33. Boland CR, Goel A ePub Jun 2010 (2010) PMID: 20420947
34. Samstein RM, Lee CH, Shoushtari AN, et al. ePub 02 2019 (2019) PMID: 30643254
35. Goodman AM, Kato S, Bazhenova L, et al. ePub 11 2017 (2017) PMID: 28835386
36. Goodman AM, Sokol ES, Frampton GM, et al. ePub Oct 2019 (2019) PMID: 31405947
37. Cristescu R, Mogg R, Ayers M, et al. ePub 10 2018 (2018) PMID: 30309915
38. Legrand et al., 2018; ASCO Abstract 12000
39. Chalmers ZR, Connelly CF, Fabrizio D, et al. ePub 04 2017 (2017) PMID: 28420421
40. Strickland KC, Howitt BE, Shukla SA, et al. ePub Mar 2016 (2016) PMID: 26871470
41. Pfeifer GP, You YH, Besaratinia A 571 (1-2):19-31 (2005) PMID: 15748635
42. Hill VK, Gartner JJ, Samuels Y, et al. ePub 2013 (2013) PMID: 23875803
43. Pfeifer GP, Denissenko MF, Olivier M, et al. 21 (48):7435-51 (2002) PMID: 12379884
44. Rizvi NA, Hellmann MD, Snyder A, et al. ePub Apr 2015 (2015) PMID: 25765070
45. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. ePub May 2013 (2013) PMID: 23636398
46. Briggs S, Tomlinson I ePub Jun 2013 (2013) PMID: 23447401
47. Heitzer E, Tomlinson I ePub Feb 2014 (2014) PMID: 24583393
48. null ePub Jul 2012 (2012) PMID: 22810696
49. Roberts SA, Gordenin DA ePub 12 2014 (2014) PMID: 25568919
50. Dombi E, Baldwin A, Marcus LJ, et al. ePub 12 2016 (2016) PMID: 28029918
51. Fangusaro et al., 2017; ASCO Abstract 10504
52. Ameratunga M, McArthur G, Gan H, et al. ePub Jun 2016 (2016) PMID: 26936308
53. Woodfield SE, Zhang L, Scorsone KA, et al. ePub Mar 2016 (2016) PMID: 26925841
54. Jousma E, Rizvi TA, Wu J, et al. ePub Oct 2015 (2015) PMID: 25907661
55. Nissan MH, Pratilas CA, Jones AM, et al. ePub Apr 2014 (2014) PMID: 24576830
56. Jessen WJ, Miller SJ, Jousma E, et al. ePub Jan 2013 (2013) PMID: 23221341
57. Chang T, Krisman K, Theobald EH, et al. ePub Jan 2013 (2013) PMID: 23221337
58. See WL, Tan IL, Mukherjee J, et al. ePub Jul 2012 (2012) PMID: 22573716
59. Lim SM, Park HS, Kim S, et al. ePub Mar 2016 (2016) PMID: 26859683
60. Weiss B, Widemann BC, Wolters P, et al. ePub Apr 2015 (2015) PMID: 25314964
61. Janku F, Kaseb AO, Tsimberidou AM, et al. ePub May 2014 (2014) PMID: 24931142
62. Johannessen CM, Johnson BW, Williams SM, et al. 18 (1):56-62 (2008) PMID: 18164202
63. Johannessen CM, Reczek EE, James MF, et al. 102 (24):8573-8 (2005) PMID: 15937108
64. Malone CF, Fromm JA, Maertens O, et al. ePub Sep 2014 (2014) PMID: 24913553
65. Tolcher AW, Bendell JC, Papadopoulos KP, et al. ePub Jan 2015 (2015) PMID: 25344362
66. Patterson et al., 2018; AACR Abstract 3891
67. Ross JS, Ali SM, Wang K, et al. ePub Sep 2013 (2013) PMID: 23791828
68. Sangha N, Wu R, Kuick R, et al. ePub Dec 2008 (2008) PMID: 19048115
69. Schwarz RF, Ng CK, Cooke SL, et al. ePub Feb 2015 (2015) PMID: 25710373
70. Patch AM, Christie EL, Etemadmoghadam D, et al. ePub May 2015 (2015) PMID: 26017449
71. Walton JB, Farquharson M, Mason S, et al. ePub Dec 2017 (2017) PMID: 29203787
72. Hattori S, Ohmi N, Maekawa M, et al. 177 (1):83-9 (1991) PMID: 1904223
73. Morcos P, Thapar N, Tusneem N, et al. 16 (5):2496-503 (1996) PMID: 8628317
74. Ballester R, Marchuk D, Boguski M, et al. 63 (4):851-9 (1990) PMID: 2121371
75. Xu GF, O'Connell P, Viskochil D, et al. 62 (3):599-608 (1990) PMID: 2116237
76. Martin GA, Viskochil D, Bollag G, et al. 63 (4):843-9 (1990) PMID: 2121370
77. Thomas L, Richards M, Mort M, et al. ePub Dec 2012 (2012) PMID: 22807134
78. Skuse GR, Cappione AJ 6 (10):1707-12 (1997) PMID: 9300663
79. Messiaen LM, Callens T, Roux KJ, et al. 1 (6):248-53 (null) PMID: 11258625
80. Ars E, Serra E, García J, et al. 9 (2):237-47 (2000) PMID: 10607834
81. Messiaen LM, Wimmer K ePub May 2005 (2005) PMID: 15863657
82. Poullet P, Lin B, Esson K, et al. 14 (1):815-21 (1994) PMID: 8264648
83. Jett K, Friedman JM ePub Jan 2010 (2010) PMID: 20027112
84. Patil S, Chamberlain RS ePub 2012 (2012) PMID: 22240541
85. Evans DG, Huson SM, Birch JM ePub Oct 2012 (2012) PMID: 23036231
86. Upadhyaya M, Maynard J, Osborn M, et al. 32 (9):706-10 (1995) PMID: 8544190
87. Williams VC, Lucas J, Babcock MA, et al. ePub Jan 2009 (2009) PMID: 19117870
88. Kamnasaran D, Qian B, Hawkins C, et al. 104 (19):8053-8 (2007) PMID: 17463088
89. Fu B, Luo M, Lakkur S, et al. ePub Oct 2008 (2008) PMID: 18769116
90. Kwei KA, Bashyam MD, Kao J, et al. ePub May 2008 (2008) PMID: 18535672
91. Shen F, Li J, Cai W, et al. ePub Sep 2013 (2013) PMID: 23784465
92. Zheng R, Blobel GA ePub Dec 2010 (2010) PMID: 21779441
93. Hirai H, Arai T, Okada M, et al. ePub Apr 2010 (2010) PMID: 20107315
94. Bridges KA, Hirai H, Buser CA, et al. 17 (17):5638-48 (2011) PMID: 21799033
95. Rajeshkumar NV, De Oliveira E, Ottenhof N, et al. 17 (9):2799-806 (2011) PMID: 21389100
96. Osman AA, Monroe MM, Ortega Alves MV, et al. ePub Feb 2015 (2015) PMID: 25504633
97. Xu L, Huang CC, Huang W, et al. 1 (5):337-46 (2002) PMID: 12489850
98. Xu L, Tang WH, Huang CC, et al. 7 (10):723-34 (2001) PMID: 11713371
99. Camp ER, Wang C, Little EC, et al. ePub Apr 2013 (2013) PMID: 23470564
100. Kim SS, Rait A, Kim E, et al. ePub Feb 2015 (2015) PMID: 25240597
101. Pirollo KF, Nemunaitis J, Leung PK, et al. ePub Sep 2016 (2016) PMID: 27357628
102. Hajdenberg et al., 2012; ASCO Abstract e15010
103. Leijen S, van Geel RM, Pavlick AC, et al. ePub Dec 2016 (2016) PMID: 27601554

104. Moore et al., 2019; ASCO Abstract 5513

105. Leijen S, van Geel RM, Sonke GS, et al. ePub 12 2016 (2016) PMID: 27998224

106. Oza et al., 2015; ASCO Abstract 5506

107. Méndez E, Rodriguez CP, Kao MC, et al. 24 (12):2740-2748 (2018) PMID: 29535125

108. Ma CX, Cai S, Li S, et al. ePub Apr 2012 (2012) PMID: 22446188

109. Ahmed AA, Etemadmoghadam D, Temple J, et al. ePub May 2010 (2010) PMID: 20229506

110. Wojnarowicz PM, Oros KK, Quinn MC, et al. ePub 2012 (2012) PMID: 23029043

111. Kuhn E, Kurman RJ, Vang R, et al. ePub Feb 2012 (2012) PMID: 21990067

112. Karst AM, Drapkin R 2010 :932371 (2010) PMID: 19746182

113. Gadducci A, Guerrieri ME, Genazzani AR ePub Aug 2012 (2012) PMID: 22304686

114. Rechsteiner M, Zimmermann AK, Wild PJ, et al. ePub Oct 2013 (2013) PMID: 23965232

115. Okamoto A, Sameshima Y, Yokoyama S, et al. 51 (19):5171-6 (1991) PMID: 1680546

116. McConechy MK, Ding J, Senz J, et al. ePub Jan 2014 (2014) PMID: 23765252

117. McDaniel AS, Stall JN, Hovelson DH, et al. ePub Nov 2015 (2015) PMID: 26181193

118. Kindelberger DW, Lee Y, Miron A, et al. 31 (2):161-9 (2007) PMID: 17255760

119. Meserve EEK, Brouwer J, Crum CP ePub May 2017 (2017) PMID: 28106106

120. Kurman RJ, Shih IeM ePub Jul 2011 (2011) PMID: 21683865

121. de Graeff P, Crijns AP, de Jong S, et al. ePub Jul 2009 (2009) PMID: 19513073

122. Brown CJ, Lain S, Verma CS, et al. ePub Dec 2009 (2009) PMID: 19935675

123. Joerger AC, Fersht AR 77 :557-82 (2008) PMID: 18410249

124. Kato S, Han SY, Liu W, et al. 100 (14):8424-9 (2003) PMID: 12826609

125. Kamada R, Nomura T, Anderson CW, et al. ePub Jan 2011 (2011) PMID: 20978130

126. Landrum MJ, Lee JM, Benson M, et al. ePub 01 2018 (2018) PMID: 29165669

127. Bougeard G, Renaux-Petel M, Flaman JM, et al. ePub Jul 2015 (2015) PMID: 26014290

128. Sorrell AD, Espenschied CR, Culver JO, et al. ePub Feb 2013 (2013) PMID: 23355100

129. Nichols KE, Malkin D, Garber JE, et al. 10 (2):83-7 (2001) PMID: 11219776

130. Kleihues P, Schäuble B, zur Hausen A, et al. 150 (1):1-13 (1997) PMID: 9006316

131. Gonzalez KD, Noltner KA, Buzin CH, et al. ePub Mar 2009 (2009) PMID: 19204208

132. Lalloo F, Varley J, Ellis D, et al. 361 (9363):1101-2 (2003) PMID: 12672316

133. Mandelker D, Donoghue M, Talukdar S, et al. ePub 08 2019 (2019) PMID: 31050713

134. Coleman et al., 2016; ASCO Abstract 5540

135. González-Martín A, Pothuri B, Vergote I, et al. ePub Sep 2019 (2019) PMID: 31562799

136. Sandhu SK, Schelman WR, Wilding G, et al. ePub Aug 2013 (2013) PMID: 23810788

137. Konstantinopoulos PA, Waggoner S, Vidal GA, et al. ePub Jun 2019 (2019) PMID: 31194228

138. Mirza et al., 2016; ASCO Abstract 5555

139. Mirza MR, Åvall Lundqvist E, Birrer MJ, et al. ePub Oct 2019 (2019) PMID: 31474354

140. Fong PC, Boss DS, Yap TA, et al. ePub Jul 2009 (2009) PMID: 19553641

141. Gelmon KA, Tischkowitz M, Mackay H, et al. ePub Sep 2011 (2011) PMID: 21862407

142. Domchek SM, Aghajanian C, Shapira-Frommer R, et al. ePub Feb 2016 (2016) PMID: 26723501

143. Matulonis UA, Penson RT, Domchek SM, et al. ePub 06 2016 (2016) PMID: 26961146

144. Fong PC, Yap TA, Boss DS, et al. ePub May 2010 (2010) PMID: 20406929

145. Moore K, Colombo N, Scambia G, et al. ePub Oct 2018 (2018) PMID: 30345884

146. Pujade-Lauraine E, Ledermann JA, Selle F, et al. ePub Sep 2017 (2017) PMID: 28754483

147. Ledermann JA, Harter P, Gourley C, et al. ePub Nov 2016 (2016) PMID: 27617661

148. Ledermann J, Harter P, Gourley C, et al. ePub Apr 2012 (2012) PMID: 22452356

149. Ledermann J, Harter P, Gourley C, et al. ePub Jul 2014 (2014) PMID: 24882434

150. Gourley et al., 2019; ESMO Abstract 998PD

151. Ray-Coquard et al., 2019; ESMO Abstract LBA2

152. Oza AM, Cibula D, Benzaquen AO, et al. ePub Jan 2015 (2015) PMID: 25481791

153. Liu JF, Barry WT, Birrer M, et al. ePub Oct 2014 (2014) PMID: 25218906

154. Oza AM, Tinker AV, Oaknin A, et al. ePub 11 2017 (2017) PMID: 28882436

155. Kristeleit R, Shapiro GI, Burris HA, et al. 23 (15):4095-4106 (2017) PMID: 28264872

156. Drew Y, Ledermann J, Hall G, et al. ePub Mar 2016 (2016) PMID: 27002934

157. Grisham et al., 2019; dx.doi.org/10.1136/ijgc-2019-IGCS.1

158. Grisham R, Moore KN, Gordon MS, et al. (2018) PMID: 29844129

159. Slosberg ED, Kang BP, Peguero J, et al. ePub Apr 2018 (2018) PMID: 29765547

160. Bendell et al., 2014; AACR Abstract CT328

161. Juric et al., 2014; ASCO Abstract 9051

162. Banerji et al., 2014; ASCO Abstract e13559

163. de Bono J, Ramanathan RK, Mina L, et al. ePub 06 2017 (2017) PMID: 28242752

164. Piha Paul et al., 2018; AACR abstract A096

165. Gershenson et al., 2019; ESMO Abstract LBA61

166. Farley J, Brady WE, Vathipadiekal V, et al. ePub Feb 2013 (2013) PMID: 23261356

167. Pejovic et al., 2015; Am J Clin Exp Obstet Gynecol 2:140-143

168. Champer M, Miller D, Kuo DY 28 :26-28 (2019) PMID: 30809568

169. Bedard PL, Tabernero J, Janku F, et al. 21 (4):730-8 (2015) PMID: 25500057