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 high grade serous carcinoma
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

Sensitivity for the detection of copy number alterations is reduced due to sample quality.

Genomic Signatures

Loss of Heterozygosity score - 27.0 %
Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Gene Alterations

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

BRCA1 S282fs*15
TP53 R273H

1 Disease relevant genes with no reportable alterations: ***BRCA2***

4 Therapies approved in the EU
0 Therapies with Lack of Response
13 Clinical Trials

GENOMIC SIGNATURES	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
Loss of Heterozygosity score - 27.0 %	Niraparib 2A	Talazoparib
	Olaparib 2A	
10 Trials *see p. 10*	Rucaparib 2A	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Genomic Signatures section	
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** see Genomic Signatures section	

GENE ALTERATIONS	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
BRCA1 - S282fs*15	Olaparib 1	Talazoparib
	Niraparib 2A	
10 Trials *see p. 13*	Rucaparib 2A	
TP53 - R273H	none	none
1 Trial *see p. 16*		

NCCN category (resistance may not be reflected in NCCN category)

GENOMIC SIGNATURE

Loss of Heterozygosity score

RESULT
27.0 %

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.

GENOMIC SIGNATURE

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].

GENOMIC SIGNATURE

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
BRCA1

ALTERATION
S282fs*15

TRANSCRIPT NUMBER
NM_007294

CODING SEQUENCE EFFECT
843_846delCTCA

POTENTIAL TREATMENT STRATEGIES

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[2-3,50-64]. Clinical response to PARP inhibitors has been reported for patients with either germline or somatic BRCA2 mutations[2,51,57,64] and for patients who were platinum-resistant or refractory[50,54,60,63]. The placebo-controlled Phase 3 VELIA trial reported significantly improved median PFS for previously untreated patients with high-grade serous ovarian carcinoma treated with veliparib plus carboplatin-paclitaxel chemotherapy followed by single-agent veliparib maintenance therapy relative to carboplatin-paclitaxel induction without maintenance therapy for BRCA-mutated (34.7 vs. 22.0 months, HR=0.44) and homologous-recombination deficient (HRD; 31.9 vs. 20.5 months, HR=0.57) populations[65]. In this study, the addition of veliparib to chemotherapy induction without veliparib maintenance did not improve median PFS (21.1 vs. 22.0 months) relative to chemotherapy induction in the BRCA-mutated (21.1 vs. 22.0 months, HR=1.22) or HRD (18.2 vs. 20.5 months, HR=1.10) cohorts[65]. In a Phase 1 monotherapy trial of the WEE1 inhibitor AZD1775 that included 9 patients with BRCA1/2-mutated solid tumors, 2 patients with BRCA1-mutated cancers (1 with ovarian serous carcinoma and 1 with oral squamous cell carcinoma) achieved PRs, and a third patient with an ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression[66].

FREQUENCY & PROGNOSIS

In the Ovarian Serous Cystadenocarcinoma TCGA dataset, BRCA1 mutation was detected in 11.4% of cases while putative homozygous deletion of BRCA1 was found in fewer than 1% of cases[15]. An analysis of ovarian tumors showed that BRCA1 alterations (including mutations, LOH, and promoter methylation) occurred in 77.6% of tumors; mutations and LOH were associated with advanced stage and concurrent TP53 mutations[67-68]. BRCA1 hypermethylation has been correlated with BRCA1 protein loss, and has been identified as a contributing factor to ovarian cancer progression[67,69]. BRCA1 mutations occur more frequently in advanced stage ovarian tumors, but also are associated with longer overall survival and with increased response to chemotherapy in patients with ovarian cancer[67,70-74]. Approximately 15% of ovarian cancers are familial; in BRCA1 or BRCA2 carriers, tumors are more likely to be Type 2 high-grade tumors[75].

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[76]. BRCA1 alterations that disrupt the ring-type zinc finger domain (amino acids 24-65) or BRCT domains (aa 1642-1855), such as observed here, are predicted to result in a loss of function[77-79]. Germline mutations in BRCA1 or BRCA2 are associated with breast-ovarian cancer familial susceptibility (BROVCA), also known as hereditary breast-ovarian cancer (HBOC)[80-81]. The lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[82], and elevated risk of other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, at a frequency range of 20-60%[83]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[82,84-89]. In the appropriate clinical context, germline testing of BRCA1 is recommended.

GENE

TP53

ALTERATION
R273H

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
818G>A

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[90-93], or p53 gene therapy and immunotherapeutics such as SGT-53[94-98] and ALT-801[99]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[100-102]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[103]. 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[104]. 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[105]. 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[106]. 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[107]. 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[108]. 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[98]. 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[109].

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%[15,110-116]. 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]. 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)[121-123]. 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[115]. 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[124].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[125]. 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[126-128]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[129-131], including sarcomas[132-134]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[135] to 1:20,000[134]. In the appropriate clinical context, germline testing of TP53 is recommended.

Niraparib

Assay findings association

BRCA1
S282fs*15

Loss of Heterozygosity score
27.0 %

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is available in the EU for the maintenance treatment of patients with relapsed high grade serous 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 clinical evidence in ovarian and breast cancers[3,54,136] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib. On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,137] . 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%[2,137] .

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[3,138] . 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)[138]. 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[54]. 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)[139]. 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)[140]. 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)[141].

Olaparib

Assay findings association

BRCA1
S282fs*15

Loss of Heterozygosity score
27.0 %

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is available in the EU as maintenance therapy for patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, Fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy, or as first-line maintenance for patients with these cancers who have a germline or somatic BRCA mutation and are in CR or PR after platinum-based chemotherapy. Olaparib is also approved to treat patients with HER2-negative advanced breast cancer and germline BRCA mutations who have been previously treated with chemotherapy; patients with hormone receptor-positive breast cancer should have been previously treated with, or considered not appropriate for, endocrine therapy.

GENE ASSOCIATION

Based on extensive clinical evidence in ovarian cancer[58-62] as well as strong clinical evidence in multiple other cancer types[50-52,58,61,142] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib. On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,137] . 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%[2,137] .

SUPPORTING DATA

Olaparib has been studied primarily for the treatment of ovarian cancer, and numerous studies have demonstrated significant clinical activity for patients with ovarian cancer harboring BRCA1/2 mutations, with response rates often significantly higher for patients with mutations than for those without[58,61] . For patients previously treated with chemotherapy, DCRs of 40-80% have been reported with olaparib, with response rates of up to 50%[58-63,143] . Two of three studies have shown significant correlation between platinum sensitivity and response to olaparib[60,63,142] . As first-line maintenance after CR or PR to prior platinum chemotherapy for patients with newly diagnosed advanced ovarian, primary peritoneal, or fallopian tube cancer and a deleterious or suspected deleterious germline or somatic BRCA1/2 mutation, olaparib significantly improved 3-year PFS relative to placebo (60%, versus 27%, HR=0.30), with estimated median PFS not yet reached after 41 months of median follow up in a Phase 3 trial[64]. As maintenance therapy in the setting of relapsed disease, olaparib significantly improved median PFS (8.4 vs. 4.8 months) and OS (29.8 vs. 27.8 months) compared to placebo for patients with platinum-sensitive, high-grade serous ovarian cancer, with the greatest benefit observed for those individuals with BRCA1/2 mutations[57,144-145] . A placebo-controlled Phase 3 study for patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer confirmed that olaparib maintenance therapy provides significant PFS benefit (19.1 vs. 5.5. months) for those who are BRCA-mutated and platinum-sensitive[56]. Combining olaparib with chemotherapy resulted in response rates up to 61%[142] and significantly longer PFS compared to chemotherapy alone[146] for patients with BRCA1/2-mutated ovarian cancer. Combining olaparib with the VEGFR inhibitor cediranib also increased the response rate and lengthened relapse-free survival for patients with platinum-sensitive ovarian cancer, compared to treatment with olaparib alone[147]. Clinical[148-149] and preclinical[150-151] studies have reported BRCA2 reversion mutations as a mechanism of olaparib resistance in ovarian cancer; similar resistance mechanisms have also been identified in prostate[152] and breast[153] cancers.

Rucaparib

Assay findings association

BRCA1
S282fs*15

Loss of Heterozygosity score
27.0 %

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is available in the EU to treat patients with platinum-sensitive relapsed or progressive BRCA mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more prior lines of platinum-based chemotherapy and who are unable to tolerate further platinum-based chemotherapy. Rucaparib is also available for the maintenance treatment of patients with platinum sensitive relapsed high-grade 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 strong clinical evidence in ovarian cancer[2,55,105] , as well as clinical data in other cancer types[55,154-155] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib. On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,137] . 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%[2,137] .

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[2,156-157] . 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[55].

THERAPIES APPROVED IN THE EU | IN OTHER TUMOR TYPE

Talazoparib

Assay findings association

BRCA1
S282fs*15

Loss of Heterozygosity score
27.0 %

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is available in the EU as monotherapy to treat patients with HER2-negative locally advanced or metastatic breast cancer with germline BRCA mutations, who have been previously treated with, or are not considered candidates for, available therapies.

GENE ASSOCIATION

On the basis of strong clinical data in breast cancer[158-160] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[161-163] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib. On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,137] . 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%[2,137] .

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[162]. 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].

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 listed in this report may not be complete and exhaustive and the therapeutic agents are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type.

IMPORTANT Clinical trials are ordered by gene and prioritized in the following descending order: Pediatric trial qualification → Geographical proximity → Trial phase → Trial verification within last 2 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. The clinical trials listed in this report may not be complete and exhaustive or may include trials for which the patient does not meet the clinical trial enrollment criteria. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov or local registries in your region.

GENOMIC SIGNATURE

Loss of Heterozygosity score

RESULT

27.0 %

RATIONALE

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

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)

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), Brașov (Romania), Bucharest (Romania), Craiova (Romania), Iași (Romania), Suceava (Romania), Timișoara (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)

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)

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)

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)

NCT03521037

PHASE 1

Rucaparib Hepatic Impairment Study in Patients With a Solid Tumor

TARGETS
PARP

LOCATIONS: Biała Podlaska (Poland), Poznań (Poland), Szczecin (Poland), Warszawa (Poland), Bratislava (Slovakia), Newcastle Upon Tyne (United Kingdom)

NCT03840200

PHASE 1/2

A Study Evaluating the Safety, Pharmacokinetics and Efficacy of Ipatasertib Administered in Combination With Rucaparib in Participants With Advanced Breast, Ovarian Cancer, and Prostate Cancer.

TARGETS
PARP, AKTs

LOCATIONS: California, Roma (Italy), Milano (Italy), Pamplona (Spain), New Jersey, Darlinghurst (Australia), Sydney (Australia), Pennsylvania, Texas, Padova (Italy), Malvern (Australia), Seoul (Korea, Republic of), Barcelona (Spain), Malaga (Spain)

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)

NCT03783949

PHASE 2

European Trial on Enhanced DNA Repair Inhibition in Ovarian Cancer

TARGETS
HSP90, PARP

LOCATIONS: Leuven (Belgium), Innsbruck (Austria), Caen (France), Bologna (Italy), Milan (Italy), Rome (Italy)

GENE
BRCA1

ALTERATION
S282fs*15

RATIONALE
BRCA1 loss or inactivating alterations may predict sensitivity to PARP inhibitors.

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)

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), Brașov (Romania), Bucharest (Romania), Craiova (Romania), Iași (Romania), Suceava (Romania), Timișoara (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)

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)

NCT02855944

PHASE 3

ARIEL4: A Study of Rucaparib Versus Chemotherapy BRCA Mutant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Patients

TARGETS
PARP

LOCATIONS: Calgary (Canada), Fortaleza (Brazil), Colorado, Manchester (United Kingdom), Georgia, Debrecen (Hungary), Brno (Czechia), Ottawa (Canada), Toronto (Canada), Curitiba (Brazil), Praha 5 (Czechia), Montreal (Canada), Montréal (Canada), Sherbrooke (Canada), Ijui (Brazil), Porto Alegre (Brazil), Barretos (Brazil), Florianópolis (Brazil), Sutton (United Kingdom), Grzepnica (Poland), Rio de Janeiro (Brazil), Sao Paulo (Brazil), Ostrava (Czechia), Praha (Czechia), Budapest (Hungary), Haifa (Israel), Holon (Israel), Jerusalem (Israel), Petach-Tikva (Israel), Tel Aviv (Israel), Tel Hashomer (Israel), Bologna (Italy), Candiolo (Italy), Catania (Italy), Milano (Italy), Modena (Italy), Napoli (Italy), Roma (Italy), Bialystok (Poland), Lublin (Poland), Olsztyn (Poland), Poznan (Poland), Szczecin (Poland), Arkhangelsk (Russian Federation), Kursk (Russian Federation), Moscow (Russian Federation), Omsk (Russian Federation), Pyatigorsk (Russian Federation), Ryazan (Russian Federation), Saint Petersburg (Russian Federation), Saint-Petersburg (Russian Federation), Saransk (Russian Federation), Sochi (Russian Federation), Ufa (Russian Federation), Barcelona (Spain), Girona (Spain), La Coruna (Spain), Madrid (Spain), Dnipropetrovsk (Ukraine), Kyiv (Ukraine), Lutsk (Ukraine), Lviv (Ukraine), Odessa (Ukraine), Sumy (Ukraine), Uzhgorod (Ukraine), Cambridge (United Kingdom), Cardiff (United Kingdom), Coventry (United Kingdom), Derby (United Kingdom), Dundee (United Kingdom), Glasgow (United Kingdom), London (United Kingdom), Middlesex (United Kingdom), Newcastle upon Tyne (United Kingdom)

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)

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)

NCT03521037

PHASE 1

Rucaparib Hepatic Impairment Study in Patients With a Solid Tumor

TARGETS
PARP

LOCATIONS: Biała Podlaska (Poland), Poznań (Poland), Szczecin (Poland), Warszawa (Poland), Bratislava (Slovakia), Newcastle Upon Tyne (United Kingdom)

NCT03565991

PHASE 2

Javelin BRCA/ATM: Avelumab Plus Talazoparib in Patients With BRCA or ATM Mutant Solid Tumors

TARGETS
PD-L1, PARP

LOCATIONS: Torette Di Ancona (Italy), California, Kashiwa (Japan), Meldola (Italy), Georgia, Louisiana, Monza (Italy), Milano (Italy), Massachusetts, Missouri, Pamplona (Spain), New Jersey, New York, Amsterdam (Netherlands), Ohio, Oklahoma, Pennsylvania, Tennessee, Texas, Chuo-ku (Japan), Rotterdam (Netherlands), Brussel (Belgium), Brussels (Belgium), Edegem (Belgium), Copenhagen (Denmark), Odense C (Denmark), Clermont Ferrand (France), La Rochelle (France), Montpellier Cedex 5 (France), Napoli (Italy), Roma (Italy), Barcelona (Spain), Madrid (Spain), Sevilla (Spain), London (United Kingdom)

NCT03840200

PHASE 1/2

A Study Evaluating the Safety, Pharmacokinetics and Efficacy of Ipatasertib Administered in Combination With Rucaparib in Participants With Advanced Breast, Ovarian Cancer, and Prostate Cancer.

TARGETS
PARP, AKTs

LOCATIONS: California, Roma (Italy), Milano (Italy), Pamplona (Spain), New Jersey, Darlinghurst (Australia), Sydney (Australia), Pennsylvania, Texas, Padova (Italy), Malvern (Australia), Seoul (Korea, Republic of), Barcelona (Spain), Malaga (Spain)

GENE
TP53

ALTERATION
R273H

RATIONALE
TP53 loss of function alterations may predict sensitivity to WEE1 inhibitors. TP53 missense mutations may predict sensitivity to therapies that reactivate mutant p53.

NCT03113487

PHASE 2

P53MVA and Pembrolizumab in Treating Patients With Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

TARGETS
PD-1, TP53

LOCATIONS: California

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.

BRCA2
S326R and T2515I

CDKN2C
T165I

FGFR1
A94T

FGFR3
G78S

KDM5A
G5E

MDM4
P388A

MYC
K443E

NTRK1
G18E

SNCAIP
Q622H

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 GENOMIC SIGNATURES

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: The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

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

Genomic Signatures and Gene Alterations
Therapies are ranked based on the following criteria: Therapies approved in the EU in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies approved in the EU in another tumor type (ranked alphabetically within each NCCN category).

Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

NCCN Categorization

Genomic signatures and gene alterations 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 genomic signature or gene alteration. 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 501x

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. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. ePub Jan 2015 (2015) PMID: 25366685
51. Mateo J, Carreira S, Sandhu S, et al. ePub Oct 2015 (2015) PMID: 26510020
52. Tutt A, Robson M, Garber JE, et al. ePub Jul 2010 (2010) PMID: 20609467
53. Robson M, Im SA, Senkus E, et al. ePub 08 2017 (2017) PMID: 28578601
54. Sandhu SK, Schelman WR, Wilding G, et al. ePub Aug 2013 (2013) PMID: 23810788
55. Drew Y, Ledermann J, Hall G, et al. ePub Mar 2016 (2016) PMID: 27002934
56. Pujade-Lauraine E, Ledermann JA, Selle F, et al. ePub Sep 2017 (2017) PMID: 28754483
57. Ledermann JA, Harter P, Gourley C, et al. ePub Nov 2016 (2016) PMID: 27617661
58. Fong PC, Boss DS, Yap TA, et al. ePub Jul 2009 (2009) PMID: 19553641
59. Audeh MW, Carmichael J, Penson RT, et al. ePub Jul 2010 (2010) PMID: 20609468
60. Fong PC, Yap TA, Boss DS, et al. ePub May 2010 (2010) PMID: 20406929
61. Gelmon KA, Tischkowitz M, Mackay H, et al. ePub Sep 2011 (2011) PMID: 21862407
62. Kaye SB, Lubinski J, Matulonis U, et al. ePub Feb 2012 (2012) PMID: 22203755
63. Domchek SM, Aghajanian C, Shapira-Frommer R, et al. ePub Feb 2016 (2016) PMID: 26723501
64. Moore K, Colombo N, Scambia G, et al. ePub Oct 2018 (2018) PMID: 30345884
65. Coleman RL, Fleming GF, Brady MF, et al. ePub Sep 2019 (2019) PMID: 31562800
66. Do K, Wilsker D, Ji J, et al. ePub Oct 2015 (2015) PMID: 25964244
67. Rzepecka IK, Szafron L, Stys A, et al. 205 (3):94-100 (2012) PMID: 22469508
68. McAlpine JN, Porter H, Köbel M, et al. ePub May 2012 (2012) PMID: 22282309
69. Wang YQ, Yan Q, Zhang JR, et al. ePub Feb 2013 (2013) PMID: 23006047
70. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, et al. ePub Jan 2008 (2008) PMID: 18165636
71. Bolton KL, Chenevix-Trench G, Goh C, et al. ePub Jan 2012 (2012) PMID: 22274685
72. McLaughlin JR, Rosen B, Moody J, et al. ePub Jan 2013 (2013) PMID: 23257159
73. Verhaak RG, Tamayo P, Yang JY, et al. ePub Jan 2013 (2013) PMID: 23257362
74. Safra T, Lai WC, Borgato L, et al. ePub Nov 2013 (2013) PMID: 24131973
75. Romero I, Bast RC ePub Apr 2012 (2012) PMID: 22416079
76. O'Donovan PJ, Livingston DM ePub Jun 2010 (2010) PMID: 20400477
77. Nelson AC, Holt JT ePub Jul 2010 (2010) PMID: 20681793
78. Silver DP, Livingston DM ePub Aug 2012 (2012) PMID: 22843421
79. Ludwig T, Fisher P, Ganesan S, et al. 15 (10):1188-93 (2001) PMID: 11358863
80. Miki Y, Swensen J, Shattuck-Eidens D, et al. 266 (5182):66-71 (1994) PMID: 7545954
81. Wooster R, Bignell G, Lancaster J, et al. 378 (6559):789-92 (null) PMID: 8524414
82. Ford D, Easton DF, Bishop DT, et al. 343 (8899):692-5 (1994) PMID: 7907678
83. null ePub Jun 2005 (2005) PMID: 16369438
84. Whittemore AS, Gong G, Itnyre J 60 (3):496-504 (1997) PMID: 9042908
85. Claus EB, Schildkraut JM, Thompson WD, et al. 77 (11):2318-24 (1996) PMID: 8635102
86. Struewing JP, Hartge P, Wacholder S, et al. 336 (20):1401-8 (1997) PMID: 9145676
87. Oddoux C, Struewing JP, Clayton CM, et al. 14 (2):188-90 (1996) PMID: 8841192
88. King MC, Marks JH, Mandell JB, et al. ePub Oct 2003 (2003) PMID: 14576434
89. Hall MJ, Reid JE, Burbidge LA, et al. 115 (10):2222-33 (2009) PMID: 19241424
90. Hirai H, Arai T, Okada M, et al. ePub Apr 2010 (2010) PMID: 20107315
91. Bridges KA, Hirai H, Buser CA, et al. 17 (17):5638-48 (2011) PMID: 21799033
92. Rajeshkumar NV, De Oliveira E, Ottenhof N, et al. 17 (9):2799-806 (2011) PMID: 21389100
93. Osman AA, Monroe MM, Ortega Alves MV, et al. ePub Feb 2015 (2015) PMID: 25504633
94. Xu L, Huang CC, Huang W, et al. 1 (5):337-46 (2002) PMID: 12489850
95. Xu L, Tang WH, Huang CC, et al. 7 (10):723-34 (2001) PMID: 11713371
96. Camp ER, Wang C, Little EC, et al. ePub Apr 2013 (2013) PMID: 23470564
97. Kim SS, Rait A, Kim E, et al. ePub Feb 2015 (2015) PMID: 25240597
98. Pirollo KF, Nemunaitis J, Leung PK, et al. ePub Sep 2016 (2016) PMID: 27357628
99. Hajdenberg et al., 2012; ASCO Abstract e15010
100. Lehmann S, Bykov VJ, Ali D, et al. ePub Oct 2012 (2012) PMID: 22965953
101. Mohell N, Alfredsson J, Fransson Å, et al. ePub Jun 2015 (2015) PMID: 26086967
102. Fransson Å, Glaessgen D, Alfredsson J, et al. ePub May 2016 (2016) PMID: 27179933
103. Gourley et al., 2016; ASCO Abstract 5571

104. Leijen S, van Geel RM, Pavlick AC, et al. ePub Dec 2016 (2016) PMID: 27601554
105. Moore et al., 2019; ASCO Abstract 5513
106. Leijen S, van Geel RM, Sonke GS, et al. ePub 12 2016 (2016) PMID: 27998224
107. Oza et al., 2015; ASCO Abstract 5506
108. Méndez E, Rodriguez CP, Kao MC, et al. 24 (12):2740-2748 (2018) PMID: 29535125
109. Ma CX, Cai S, Li S, et al. ePub Apr 2012 (2012) PMID: 22446188
110. Ahmed AA, Etemadmoghadam D, Temple J, et al. ePub May 2010 (2010) PMID: 20229506
111. Wojnarowicz PM, Oros KK, Quinn MC, et al. ePub 2012 (2012) PMID: 23029043
112. Kuhn E, Kurman RJ, Vang R, et al. ePub Feb 2012 (2012) PMID: 21990067
113. Karst AM, Drapkin R 2010 :932371 (2010) PMID: 19746182
114. Gadducci A, Guerrieri ME, Genazzani AR ePub Aug 2012 (2012) PMID: 22304686
115. Rechsteiner M, Zimmermann AK, Wild PJ, et al. ePub Oct 2013 (2013) PMID: 23965232
116. Okamoto A, Sameshima Y, Yokoyama S, et al. 51 (19):5171-6 (1991) PMID: 1680546
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. Altman AD, Nelson GS, Ghatage P, et al. ePub Sep 2013 (2013) PMID: 23558569
122. Giurgea LN, Ungureanu C, Mihailovici MS 53 (4):967-73 (2012) PMID: 23303020
123. Rajesh NG, Rekha K, Krishna B 50 (2):284-7 (2007) PMID: 17883046
124. de Graeff P, Crijns AP, de Jong S, et al. ePub Jul 2009 (2009) PMID: 19513073
125. Brown CJ, Lain S, Verma CS, et al. ePub Dec 2009 (2009) PMID: 19935675
126. Joerger AC, Fersht AR 77 :557-82 (2008) PMID: 18410249
127. Kato S, Han SY, Liu W, et al. 100 (14):8424-9 (2003) PMID: 12826609
128. Kamada R, Nomura T, Anderson CW, et al. ePub Jan 2011 (2011) PMID: 20978130
129. Bougeard G, Renaux-Petel M, Flaman JM, et al. ePub Jul 2015 (2015) PMID: 26014290
130. Sorrell AD, Espenschied CR, Culver JO, et al. ePub Feb 2013 (2013) PMID: 23355100
131. Nichols KE, Malkin D, Garber JE, et al. 10 (2):83-7 (2001) PMID: 11219776
132. Taubert H, Meye A, Würl P 4 (6):365-72 (1998) PMID: 10780879
133. Kleihues P, Schäuble B, zur Hausen A, et al. 150 (1):1-13 (1997) PMID: 9006316
134. Gonzalez KD, Noltner KA, Buzin CH, et al. ePub Mar 2009 (2009) PMID: 19204208
135. Lalloo F, Varley J, Ellis D, et al. 361 (9363):1101-2 (2003) PMID: 12672316
136. Konstantinopolous et al., 2018; ASCO Abstract 106
137. Coleman et al., 2016; ASCO Abstract 5540
138. González-Martín A, Pothuri B, Vergote I, et al. ePub Sep 2019 (2019) PMID: 31562799
139. Konstantinopoulos PA, Waggoner S, Vidal GA, et al. ePub Jun 2019 (2019) PMID: 31194228
140. Mirza et al., 2016; ASCO Abstract 5555
141. Mirza MR, Åvall Lundqvist E, Birrer MJ, et al. ePub Oct 2019 (2019) PMID: 31474354
142. Del Conte G, Sessa C, von Moos R, et al. ePub Aug 2014 (2014) PMID: 25025963
143. Matulonis UA, Penson RT, Domchek SM, et al. ePub 06 2016 (2016) PMID: 26961146
144. Ledermann J, Harter P, Gourley C, et al. ePub Apr 2012 (2012) PMID: 22452356
145. Ledermann J, Harter P, Gourley C, et al. ePub Jul 2014 (2014) PMID: 24882434
146. Oza AM, Cibula D, Benzaquen AO, et al. ePub Jan 2015 (2015) PMID: 25481791
147. Liu JF, Barry WT, Birrer M, et al. ePub Oct 2014 (2014) PMID: 25218906
148. Barber LJ, Sandhu S, Chen L, et al. ePub Feb 2013 (2013) PMID: 23165508
149. Norquist B, Wurz KA, Pennil CC, et al. ePub Aug 2011 (2011) PMID: 21709188
150. Sakai W, Swisher EM, Jacquemont C, et al. ePub Aug 2009 (2009) PMID: 19654294
151. Rytelewski M, Maleki Vareki S, Mangala LS, et al. ePub Apr 2016 (2016) PMID: 26959114
152. Quigley D, Alumkal JJ, Wyatt AW, et al. ePub 09 2017 (2017) PMID: 28450426
153. Gornstein EL, Sandefur S, Chung JH, et al. ePub 04 2018 (2018) PMID: 29325860
154. Kristeleit et al., 2014; ASCO Abstract 2573
155. Domcheck et al., 2016; ASCO Abstract 4110
156. Oza AM, Tinker AV, Oaknin A, et al. ePub 11 2017 (2017) PMID: 28882436
157. Kristeleit R, Shapiro GI, Burris HA, et al. 23 (15):4095-4106 (2017) PMID: 28264872
158. Turner et al., 2017; ASCO Abstract 1007
159. Litton JK, Rugo HS, Ettl J, et al. ePub Aug 2018 (2018) PMID: 30110579
160. Ettl J, Quek RGW, Lee KH, et al. ePub Sep 2018 (2018) PMID: 30124753
161. Meehan et al., 2017; AACR Abstract 4687
162. de Bono J, Ramanathan RK, Mina L, et al. ePub 06 2017 (2017) PMID: 28242752
163. Lu E, Thomas GV, Chen Y, et al. ePub 08 2018 (2018) PMID: 30099369
164. Piha Paul et al., 2018; AACR abstract A096

AT/ONCO/0320/0007

FOUNDATION MEDICINE® | Roche