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 Eye lacrimal duct carcinoma
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE Lacrimal Gland
SPECIMEN ID 1
SPECIMEN TYPE Block
DATE OF COLLECTION 16 April 2020
SPECIMEN RECEIVED 15 June 2020

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

Genomic Signatures

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

Gene Alterations

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

BRCA1 M1I
TP53 R175H - subclonal†

† See About the Test in appendix for details.

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

GENOMIC SIGNATURES

Microsatellite status - MS-Stable

Tumor Mutational Burden - 0 Muts/Mb

GENE ALTERATIONS

***BRCA1* -** M1I

10 Trials *see p. 8*

ACTIONABILITY

No therapies or clinical trials. see Genomic Signatures section

No therapies or clinical trials. see Genomic Signatures section

THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
none	Niraparib
	Olaparib
	Rucaparib
	Talazoparib

GENE ALTERATIONS 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 Alterations section.

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

Therapies contained in this report may have been approved through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally and may not be available in all EU Member States: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, Triptorelin.

Electronically signed by

Sample Preparation: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany
Sample Analysis: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany

Информация в данном материале предназначена для медицинских работников

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[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been observed at high frequency in endometrial cancers (16-33%)[6-13], colorectal cancers (CRCs; 10-15%)[3,14-17], and gastric cancers (12-35%)[18-21] and at lower frequencies in many other tumor types, including esophageal[22], small bowel[23-27], hepatobiliary[28-34], prostate[35-37], and urinary tract carcinomas[38-40]. The prognostic significance of MSI in lacrimal duct carcinoma is unknown (PubMed, Feb 2020).

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[16]. 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[16,41-42]. 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[15,43-44]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15-16,42,44].

BIOMARKER

Tumor Mutational Burden

RESULT
0 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[45-47] and anti-PD-1 therapies[45-48]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[45-48]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[45]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[49] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[46]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in patients with TMB ≥10 Muts/Mb compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[48]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Studies of TMB in the context of head and neck cancers have been focused on head and neck squamous cell carcinoma; eye lacrimal duct carcinomas have not been evaluated for TMB (PubMed, Feb 2020). Published data investigating the prognostic implications of TMB in eye lacrimal duct carcinoma are limited (PubMed, Feb 2020).

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[50-51] and cigarette smoke in lung cancer[52-53], treatment with temozolomide-based chemotherapy in glioma[54-55], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[17,56-59], and microsatellite instability (MSI)[17,56,59]. 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[46-47].

GENE
BRCA1

ALTERATION
M1I

TRANSCRIPT NUMBER
NM_007294

CODING SEQUENCE EFFECT
3G>C

POTENTIAL TREATMENT STRATEGIES

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[60-77] or to ATR inhibitors[78-79]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[61,66,69,76-77] and for patients with platinum-resistant or -refractory disease[60,65,72,75]. In a Phase 1 monotherapy trial of the WEE1 inhibitor adavosertib 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 ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression[80]. In a Phase 1 trial of monotherapy treatment with the ATR inhibitor BAY1895344, 2 patients with deleterious BRCA1 alterations and either platinum-refractory peritoneal or ovarian carcinoma experienced a PR or prolonged SD[81]. In other Phase 1 trials of combination approaches, a patient with BRCA1-mutated ovarian carcinoma experienced prolonged SD from the ATR inhibitor berzosertib combined with topotecan[78]; another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin[82]; and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib[83]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[84], ovarian carcinoma[85], and TNBC[86] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

BRCA1 mutation has not been reported in any of the 96 adenocarcinomas of the upper aerodigestive tract analyzed in COSMIC (May 2020)[87]. A study of nasopharyngeal carcinomas (NPC) reported limited correlation between BRCA1 expression and distant metastasis-free survival[88]. A preclinical study of cisplatin resistant NPC cells reported that BRCA1 depletion restores sensitivity to cisplatin[89].

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[90]. BRCA1 missense mutations affecting amino acid M1, such as observed here, may disrupt expression or lead to transcription initiation from the alternative M18 generating isoform 4 or deltaBRCA1(17aa)[91]; therefore, the functional consequences of this alteration are unclear. BRCA1 M1T, M1I, and M1V have been described in the ClinVar database as pathogenic germline mutations associated with hereditary breast and ovarian cancer syndrome (ClinVar, Mar 2020)[92]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[93-94], and 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[95]. Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%[96]. 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[95,97-102]. In the appropriate clinical context, germline testing of BRCA1 is recommended.

GENE
TP53

ALTERATION
R175H - subclonal

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
524G>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[103-106], or p53 gene therapy and immunotherapeutics such as SGT-53[107-111] and ALT-801[112]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[113]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[114]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[115]. 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[116]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[117]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[118]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[111]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[119]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[120-122]. 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[123]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[124-125]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[126-127]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutation was not seen in the single eye lacrimal duct carcinoma analyzed in the COSMIC database (Feb 2020)[87], nor in any of 11 eye lacrimal adenoid cystic carcinomas analyzed in one whole exome sequencing analysis[128]. TP53 loss has not been a significant topic of investigation in eye lacrimal duct carcinoma in the literature (cBioPortal, PubMed, Feb 2020)[129-130]. Published data investigating the prognostic implications of TP53 alterations in eye lacrimal duct carcinoma are limited (PubMed, Feb 2020).

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[131]. 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[132-134]. One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with Li-Fraumeni syndrome (ClinVar, Mar 2020)[92]. 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[135-137], including sarcomas[138-139]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[140] to 1:20,000[139]. 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[141]. In the appropriate clinical context, germline testing of TP53 is recommended.

Niraparib

Assay findings association

BRCA1
M1I

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. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian and breast cancers[64-65,142] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of head and neck carcinoma are limited (PubMed, Feb 2020). Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[64]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[65]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[143].

Olaparib

Assay findings association

BRCA1
M1I

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. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in ovarian cancer[70-74] as well as strong clinical evidence in multiple other cancer types[60-62,70,73,77,144] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Clinical data on the efficacy of olaparib for the treatment of head and neck carcinoma are limited (PubMed, Feb 2020). Olaparib has been studied primarily for the treatment of ovarian cancer, with response rates often significantly higher for patients with BRCA mutations than for those without[70,73] , and for patients with platinum-sensitive versus platinum-resistant cancer[72-73,75,145] . As a maintenance therapy for patients with newly diagnosed or platinum-sensitive relapsed ovarian cancer, olaparib has demonstrated significantly improved median PFS and median OS compared to placebo in the Phase 3 SOLO-1 study[76] and multiple later-phase studies[68-69,146-147] . Phase 3 studies of olaparib for patients with BRCA-mutated metastatic breast[63] or pancreatic cancer[77] or for patients with metastatic castration-resistant prostate cancer and BRCA or ATM alterations[148] have also reported significantly longer median PFS compared to chemotherapy, placebo, or hormonal therapy. Olaparib has also demonstrated clinical activity for patients with other solid tumors harboring BRCA mutations, including leiomyosarcoma[149], cholangiocarcinoma[150], and bladder cancer[151] in smaller studies.

Rucaparib

Assay findings association

BRCA1
M1I

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. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence in ovarian cancer[66-67,114] , as well as clinical data in other cancer types[67,152-153] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of head and neck carcinoma are limited (PubMed, Feb 2020). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[66]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[114]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[67]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[152]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[153]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[154]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[155]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[156].

Talazoparib

Assay findings association

BRCA1
M1I

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. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data in breast cancer[157-159] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[160-162] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Talazoparib has been studied primarily in the context of BRCA-mutated, HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study[158-159] . In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration[163]. Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer[160-162,164] .

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.

NOTE 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.

GENE
BRCA1

ALTERATION
M1I

RATIONALE
BRCA1 loss or inactivating alterations may predict sensitivity to PARP inhibitors or ATR inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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: Moscow (Russian Federation), Ryazan (Russian Federation), Saint-Petersburg (Russian Federation), St.Petersburg (Russian Federation), Saint Petersburg (Russian Federation), Kazan (Russian Federation), Samara (Russian Federation), Arkhangelsk (Russian Federation), Cluj Napoca (Romania), Cluj napoca (Romania)

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Kharkiv (Ukraine), Daugavpils (Latvia), Cherkasy (Ukraine), Dnipro (Ukraine), Riga (Latvia), Zhytomyr (Ukraine), Kropyvnytsky (Ukraine), Zaporizhzhia (Ukraine), Vinnytsia (Ukraine), Khmelnitskiy (Ukraine)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT03127215

PHASE 2

Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors

TARGETS
FUS-DDIT3, PARP

LOCATIONS: Heidelberg (Germany)

NCT03188965

PHASE 1

First-in-human Study of ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas

TARGETS
ATR

LOCATIONS: St. Gallen (Switzerland), Bellinzona (Switzerland), Genève (Switzerland), Newcastle Upon Tyne (United Kingdom), Sutton (United Kingdom), Cardiff (United Kingdom), Quebec (Canada), Ottawa (Canada), Massachusetts, Kashiwa (Japan)

CLINICAL TRIALS

NCT02278250

PHASE 1

An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-803/M4344 as a Single Agent and in Combination With Cytotoxic Chemotherapy in Participants With Advanced Solid Tumors

TARGETS
ATR

LOCATIONS: Rotterdam (Netherlands), London (United Kingdom), Sutton (United Kingdom), Barcelona (Spain), Valencia (Spain), Madrid (Spain), Massachusetts, New Jersey, Michigan, Wisconsin

NCT04170153

PHASE 1

M1774 in Participants With Metastatic or Locally Advanced Unresectable Solid Tumors

TARGETS
ATR

LOCATIONS: Sutton (United Kingdom), Texas

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT03641547

PHASE 1

M6620 Plus Standard Treatment in Oesophageal and Other Cancer

TARGETS
ATR

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

NCT04171700

PHASE 2

A Study to Evaluate Rucaparib in Patients With Solid Tumors and With Deleterious Mutations in HRR Genes

TARGETS
PARP

LOCATIONS: Massachusetts, New York, Pennsylvania, Iowa, Washington, Tennessee

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.

CCND1
V109A

FLT1
exon 19 deletion (S733del)

PIK3CB
D16N

PTPRO
A11S

ROS1
K1029E

SMO
R726Q

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.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Genomic signatures and gene alterations detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each 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®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. 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

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The median exon coverage for this sample is 1,235x

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