FOUNDATIONONE®CDx

PATIENT
Peng, Nen-Ping

TUMOR TYPE
Ovary epithelial carcinoma (NOS)
COUNTRY CODE
TW

REPORT DATE
23 Aug 2022
ORDERED TEST #
ORD-1433069-01

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

PATIENT
DISEASE Ovary epithelial carcinoma (NOS)
NAME Peng, Nen-Ping
DATE OF BIRTH 25 September 1955
SEX Female
MEDICAL RECORD # 34913661

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Lymph Node
SPECIMEN ID S111-19890 A (PF22089)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 17 May 2022
SPECIMEN RECEIVED 13 August 2022

Biomarker Findings

Loss of Heterozygosity score - 21.8%
Homologous Recombination status - HRD Positive
Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings

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

BRCA2 S780*
MYC amplification - equivocal†
NF2 E90fs*9
TP53 R156P
MSH6 S1094fs*6

1 Disease relevant genes with no reportable alterations: ***BRCA1***

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Niraparib** (p. 9), **Olaparib** (p. 10), **Rucaparib** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***BRCA2*** **S780*** (p. 5)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Loss of Heterozygosity score - 21.8%	Niraparib 2A	Talazoparib
10 Trials *see p. 13*	Olaparib 2A	
	Rucaparib 2A	
Homologous Recombination status - HRD Positive	**HRD Positive defined as presence of deleterious *BRCA1/2* alteration and/or LOH score ≥ 16% (Coleman et al., 2017; 28916367).**	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRCA2 - S780*	Niraparib [1]	Talazoparib
	Olaparib [1]	
10 Trials *see p. 15*	Rucaparib [1]	
MYC - amplification - equivocal	none	none
5 Trials *see p. 17*		
NF2 - E90fs*9	none	none
10 Trials *see p. 18*		
TP53 - R156P	none	none
2 Trials *see p. 20*		

[ ] *NCCN category*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

BRCA2 - S780* ..... p. 5

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

MSH6 - S1094fs*6 ..... p. 8

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

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

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BIOMARKER

Loss of Heterozygosity score

RESULT
21.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

The loss of heterozygosity (LOH) score is a profile of the percentage of the tumor genome that is under focal loss of one allele[2]; focal LOH events accumulate as genomic "scars" as a result of incorrect DNA double-strand break repair when the homologous recombination pathway is deficient (HRD)[6,10,13-14]. HRD and consequent genomic LOH occur as a result of genetic or epigenetic inactivation of one or more of the homologous recombination pathway proteins, including BRCA1, BRCA2, RAD51C, ATM, PALB2, and BRIP1[13-16]. This sample harbors a genomic LOH score that has been shown to be associated with sensitivity to the PARP inhibitor rucaparib in platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma in both the treatment[2] and maintenance[1] settings.

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[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], and 10.0% (3/30) of ovarian clear cell carcinomas (CCOCs)[25]. No association of MSI-H with stage or survival was found in patients with ovarian cancer[22,26].

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[27]. 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[27-29]. 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[30-32]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[27,29,31-32].

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BIOMARKER

Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[33-35], anti-PD-1 therapies[33-36], and combination nivolumab and ipilimumab[37-42]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[33-36,43-47]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[43]; similar findings were observed in the KEYNOTE 028 and 012 trials[36]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[47]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[48]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[46]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[49] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[34].

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)[50]. 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[51].

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[52-53] and cigarette smoke in lung cancer[54-55], treatment with temozolomide-based chemotherapy in glioma[56-57], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[58-62], and microsatellite instability (MSI)[58,61-62]. 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[34-35,43].

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GENE
BRCA2

ALTERATION
S780*

TRANSCRIPT ID
NM_000059

CODING SEQUENCE EFFECT
2339C>G

VARIANT ALLELE FREQUENCY (% VAF)
58.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[2-3,63-78] or ATR inhibitors[79-81]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[2,64,70,77-78] and for patients with platinum-resistant or -refractory disease[63,67,73,76]. In a case study, a patient with therapy-induced neuroendocrine prostate cancer and an inactivating BRCA2 rearrangement experienced a CR ongoing for 20 months to the ATR inhibitor berzosertib[81]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[82], ovarian carcinoma[83], and triple-negative breast cancer (TNBC)[84] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA2-deficient cells to ATR inhibitors. The placebo-controlled Phase 3 VELIA trial reported a 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[85]. In this study, the addition of veliparib to chemotherapy induction without veliparib maintenance did not improve the 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[85]. WEE1 inhibitor adavosertib has been evaluated as a monotherapy and in combination with PARP-inhibitor, olaparib. In a Phase 2 study for patients with PARP-resistant ovarian cancer, the combination of olaparib and adavosertib elicited improved clinical benefit (ORR 29%, DCR 89%) compared to adavosertib alone (ORR 23%, DCR 63%); however, in the BRCA-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR 19%) and monotherapy (ORR 20%) treatments[86]. In phase 1 study, 1 of 4 patients with BRCA1 or BRCA2 mutated serous ovarian cancer achieved a PR[87].

— Nontargeted Approaches —

Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as trabectedin, lurbinectedin, and the platinum chemotherapies cisplatin and carboplatin[8,88-97]. Alterations in DNA repair genes such as BRCA1, BRCA2, ATM, BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C, and RAD51D have been reported to be predictive for sensitivity to platinum agents and improved overall survival in stage 2–4 ovarian, fallopian tube, and peritoneal carcinomas (P = 0.0006)[98].

FREQUENCY & PROGNOSIS

In the TCGA dataset, BRCA2 mutation was found in 11% of ovarian serous cystadenocarcinoma cases[15]. A meta-analysis of ovarian carcinoma studies showed germline and somatic BRCA2 alterations to be most prevalent in high-grade serous carcinomas but present at lower frequencies in tumors with endometrioid, clear cell, mucinous, carcinosarcoma, and low-grade serous histologies[99]. A retrospective meta-analysis of 10,000 patients with ovarian serous carcinoma associated BRCA2 mutation with improved OS (HR=0.58) and PFS (HR=0.61)[100]. One study reported prolonged 5-year PFS for patients with ovarian cancer and a BRCA2 mutation in the RAD51-binding domain (exon 11) compared to those with either BRCA2 mutations in other domains or with BRCA2 wildtype status[101].

FINDING SUMMARY

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[102]. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis[103]. Alterations such as seen here may disrupt BRCA2 function or expression[102,104-119].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the BRCA2 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Mar 2022)[120]. 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[121-122], and the lifetime risk of breast and ovarian cancer in BRCA2 mutation carriers has been estimated to be as high as >80% and 23%, respectively[123]. 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%[124]. 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[123,125-130]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

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GENE
MYC

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data indicate MYC overexpression may predict sensitivity to investigational agents targeting CDK1[131-132], CDK2[133], Aurora kinase A[134-141], Aurora kinase B[142-145], glutaminase[146-149], or BET bromodomain-containing proteins[150-153], as well as agents targeting both HDAC and PI3K[154-156]. Exploratory biomarker analysis in a Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer but not for patients without MYC overexpression[157]. A PR was reported for a patient with MYC-amplified invasive ductal breast carcinoma treated with an unspecified Aurora kinase inhibitor and taxol[158].

— Nontargeted Approaches —

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[159-160]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[161-162].

FREQUENCY & PROGNOSIS

Amplification of the MYC gene has been identified in 25-60% of ovarian tumors[15,163-166]. Overexpression of the MYC protein has been observed in 66% (31/47) of ovarian epithelial tumors[167]. For patients with ovarian carcinoma, MYC amplification has been associated with increased malignancy, higher histological grade, and poorer overall survival[166,168].

FINDING SUMMARY

MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[169]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[170]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[169,171-172].

GENE
NF2

ALTERATION
E90fs*9

TRANSCRIPT ID
NM_000268

CODING SEQUENCE EFFECT
268_340del73

VARIANT ALLELE FREQUENCY (% VAF)
8.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

NF2 inactivating alterations may indicate sensitivity to mTOR inhibitors[173-176]. Two case studies reported clinical benefit for patients with NF2-mutated cancers, including urothelial carcinoma[177] and metaplastic breast cancer[158,178] treated with everolimus and temsirolimus, respectively. Loss or inactivation of NF2 may also predict sensitivity to FAK inhibitors based on clinical data in mesothelioma[179] and meningioma[180] and strong preclinical data[181-183]. Limited preclinical and clinical evidence in vestibular schwannoma suggests possible sensitivity of NF2-deficient tumors to the pan-ERBB inhibitor lapatinib[184-185]. Similarly, on the basis of limited clinical[186] and preclinical[187-189] evidence, NF2 inactivation may predict sensitivity to MEK inhibitors, such as approved agents trametinib and cobimetinib. These and other relevant compounds are being investigated in clinical trials. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[190], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[191].

FREQUENCY & PROGNOSIS

In the Ovarian Serous Cystadenocarcinoma TCGA datasets, NF2 mutation or homozygous deletion was observed in fewer than 1% of cases[15]. No significant relationship was identified between Merlin expression levels and grade, stage, or overall survival of patients with serous ovarian cancer, although low Merlin mRNA expression correlated with increased survival in cohorts that were optimally-debulked or treated with platinum plus taxol[183].

FINDING SUMMARY

Merlin, encoded by NF2, coordinates cell contact with growth signals; the inactivation of Merlin disrupts this mechanism and can lead to unrestrained growth despite cell contact[192]. Alterations such as seen here may disrupt NF2 function or expression[193-199].

POTENTIAL GERMLINE IMPLICATIONS

Heterozygous germline NF2 loss or inactivation is associated with neurofibromatosis type 2, which results in the development of vestibular schwannomas, meningiomas, ependymomas, and ocular disturbances[200-202]. Prevalence for this disorder in the general population is estimated to be 1:25,000[202]. In the appropriate clinical context, germline testing of NF2 is recommended.

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GENE
TP53

ALTERATION
R156P

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
467G>C

VARIANT ALLELE FREQUENCY (% VAF)
21.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[203-206], or p53 gene therapy and immunotherapeutics such as SGT-53[207-211] and ALT-801[212]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[213]. 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 for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[214]. 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 for patients with platinum-refractory TP53-mutated ovarian cancer[215]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[216]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[217]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[218]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[219]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[211]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[220-222]. In a Phase 1b trial for 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[223]. 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[224-225]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[226-227]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

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%[15,228-234]. One study reports TP53 mutation in all subtypes of ovarian carcinoma, including 57% (8/14) of mucinous, 28% (8/29) of high grade endometrioid, and 52% (13/25) of clear cell cases[233]. One study reported TP53 mutation in 6.7% of low grade ovarian endometrioid carcinomas[235]. 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[233]. 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[236].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[237]. Alterations such as seen here may disrupt TP53 function or expression[238-242].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[243-245], including sarcomas[246-247]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[248] to 1:20,000[247]. 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[249]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[250-255]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[250-251]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[256]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[254,257-258]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
MSH6

ALTERATION
S1094fs*6

TRANSCRIPT ID
NM_000179

CODING SEQUENCE EFFECT
3280_3335del56

VARIANT ALLELE FREQUENCY (% VAF)
7.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Numerous studies in various cancer types have shown that MSH6 loss or inactivation is associated with MSI and increased mutation burden[28,61,259-262]. Clinical studies have shown that MSI is associated with patient responses to anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[20,263] and nivolumab[264]. Higher mutation burden was also reported to be associated with response to pembrolizumab[55]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[17], potential biomarkers of response to PD-1 targeted immunotherapies. Therefore, inactivation of MSH6 may confer sensitivity to anti-PD-1 immune checkpoint inhibitors.

FREQUENCY & PROGNOSIS

MSH6 mutations have been reported in 2.1% of ovarian carcinoma tumors analyzed in the COSMIC database (Mar 2022)[265]. In the TCGA ovarian serous cystadenocarcinoma dataset MSH6 mutation was found in <1% of patients[15]. The risk of ovarian cancer associated with mutations in MSH6 (approximately 1%) has been reported to be lower than that associated with mutations in MLH1 or MSH2 (12% and 16%, respectively)[266].

FINDING SUMMARY

MSH6 encodes MutS homolog 6 protein, a member of the mismatch repair (MMR) gene family. Defective MMR occurring as a result of mutation(s) in the MMR family (MLH1, MSH2, MSH6, or PMS2) can result in microsatellite instability (MSI), common in colon, endometrium, and stomach cancers[28]. Alterations such as seen here may disrupt MSH6 function or expression[267-272].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in MSH6 are associated with both "typical" and "atypical" forms of autosomal dominant Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC), which accounts for 1-7% of all colorectal cancers[273]. Approximately 10% of all Lynch syndrome-associated mutations have been attributed to alterations in MSH6[274]. Carriers of mutations in MSH6 have a 60-80% risk of colorectal cancer[275]. Lynch syndrome has an estimated prevalence in the general population ranging from 1:600 to 1:2000[273,276-277]. Biallelic germline mutation of MSH6 has been shown to account for 20% of cases of the very rare syndrome Constitutional Mismatch Repair Deficiency (CMMRD), which is characterized by a 95% incidence rate of childhood onset lymphoma, leukemia and brain tumors, followed by early-onset colorectal cancer[278-282]. Given the association between MSH6 and these inherited syndromes, in the appropriate clinical context, germline testing of MSH6 is recommended.

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Niraparib

Assay findings association

BRCA2
S780*

Loss of Heterozygosity score
21.8%

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,283] . 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%[2,283] . On the basis of clinical evidence in ovarian and breast cancers[3,67,284] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib.

SUPPORTING DATA

In a Phase 1 study of niraparib treatment for patients with advanced solid tumors, 40% (8/20) of patients with BRCA1/2-mutated ovarian cancer experienced a PR[67]. For patients with platinum-sensitive, recurrent ovarian cancer (OC), the Phase 3 ENGOT-OV16/NOVA study showed that niraparib maintenance therapy significantly increased median PFS (mPFS) relative to placebo, regardless of germline BRCA (gBRCA) mutation (21.0 vs. 5.5 months, HR=0.27 for patients with gBRCA mutations; 9.3 vs. 3.9 months, HR=0.45 for patients without gBRCA mutations) or homologous recombination deficiency (HDR) status (12.9 vs. 3.8 months, HR=0.38)[3,285] . Similarly, the Phase 3 PRIMA trial for patients with newly diagnosed advanced OC reported an extended mPFS from niraparib maintenance therapy after response to first-line platinum chemotherapy compared with placebo (13.8 vs. 8.2 months, HR=0.62); subgroup analysis showed that patients with HRD-positive OC experienced the longest mPFS, which was irrespective of BRCA mutational status (21.9 vs. 10.4 months, HR=0.43)[286]. The Phase 2 QUADRA study evaluating niraparib monotherapy as late-line treatment for patients with relapsed high-grade serous epithelial ovarian cancer (HGSOC) reported a median OS (mOS) of 12.2 months for all HGSOC patients, with highest mOS seen for those with BRCA1/2-mutated and HRD-positive tumors (26.0 and 19.0 months, respectively)[287]. A Phase 2 trial for patients with platinum-sensitive HGSOC and endometrioid recurrent ovarian cancer reported significantly improved mPFS from the addition of bevacizumab to niraparib compared with niraparib alone (11.9 vs. 5.5 months, HR=0.35)[288]. In a Phase 1/2 study of niraparib in combination with pembrolizumab for patients with recurrent platinum-resistant OC, patients experienced an ORR of 19% (11/59) and mPFS of 3.4 months; no significant differences in ORR were noted among analyzed subgroups: 14% (3/21) versus 19% (6/32) for patients with HRD-positive versus HRD-negative tumors, 18% (2/11) versus 19% (9/47) for patients with BRCA-mutated versus BRCA-wildtype tumors, and 21% (7/33) versus 10% (2/21) for patients with PD-L1-positive versus PD-L1-negative tumors[289].

Olaparib

Assay findings association

BRCA2
S780*

Loss of Heterozygosity score
21.8%

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,283] . 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%[2,283] . On the basis of extensive clinical evidence in ovarian cancer[71-75] as well as strong clinical evidence in multiple other cancer types[63-65,71,74,78,290] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib.

SUPPORTING DATA

The Phase 3 SOLO3 trial of olaparib monotherapy for pretreated patients with germline BRCA1/2-mutated relapsed ovarian cancer observed improved ORRs in the olaparib group compared with the chemotherapy-treated group (72% vs. 51%)[291]. A final analysis observed similar OS rates between groups (34.9 vs. 32.9 months), numerically improved second PFS (23.6 vs. 19.6 months), and clinically meaningful delays in time to first or second subsequent therapy (TFST or TSST) or death for the olaparib group (TFST, 15.4 vs. 10.9 months; TSST, 25.2 vs. 19.9 months)[292]. Phase 2 studies reported clinical benefit for patients with BRCA1/2-mutated heavily pretreated platinum-resistant and platinum-sensitive ovarian cancer from the combination of olaparib with cediranib or durvalumab[293-294] . Patients with platinum-sensitive, recurrent BRCA1/2-mutated high grade serous ovarian cancer (HGSOC) treated with olaparib monotherapy or olaparib in combination with chemotherapy experienced a statistically superior median PFS compared with controls in the maintenance setting[295-296] ; clinical benefit was also reported for patients with platinum-resistant advanced BRCA1/2-mutated HGSOC following olaparib monotherapy treatment[74]. A retrospective pooled analysis of Phase 1 and Phase 2 studies of olaparib monotherapy for patients with germline BRCA1/2 (gBRCA1/2) mutation-positive advanced relapsed ovarian cancer who progressed on prior lines of chemotherapy reported an ORR of 36% and duration of response of 7.4 months[297]. A Phase 1 study of olaparib in combination with liposomal doxorubicin for patients with metastatic ovarian cancer reported an ORR of 61% (11/18) for patients with gBRCA1/2 mutations[290]. In a Phase 2 study of olaparib plus pembrolizumab for advanced solid tumors, patients with BRCA1 or BRCA2 mutations achieved an ORR of 29% (6/21), whereas patients with mutations in other homologous recombination repair genes achieved an ORR of 6.3% (2/32)[298]. Olaparib has been studied primarily to treat patients with ovarian cancer harboring BRCA1/2 mutations. Numerous Phase 2 studies have demonstrated significant clinical activity for patients with BRCA-mutated ovarian cancer, with response rates often significantly higher for patients with BRCA mutations than for those without[71,74] , and for patients with platinum-sensitive (vs. platinum-resistant) cancer[73-74,76,297] . As maintenance therapy for patients with newly diagnosed or platinum-sensitive relapsed ovarian cancer, olaparib monotherapy demonstrated significantly improved median PFS (mPFS) and OS compared with placebo in the Phase 3 SOLO-1 study[77] and multiple later-phase studies[69-70,295,299-300] . At the 5-year follow-up of SOLO-1, olaparib continued to improve mPFS compared with placebo for patients with ovarian cancer[301]. In the first study of PARPi rechallenge for patients with ovarian cancer, the Phase 3 OReO/ENGOT Ov-38 study of maintenance olaparib compared with placebo reported statistically improved mPFS for both patients with BRCA-mutated (4.3 vs. 2.8 months, HR=0.57) and BRCA-unmutated (5.3 vs. 2.8 months, HR=0.43) cancer; in an exploratory analysis of the BRCA-unmutated cohort, improved mPFS was reported regardless of homologous recombination deficiency status[302]. Olaparib has also been evaluated in combination with other therapies. A statistically superior median PFS from treatment with olaparib in combination with the VEGF inhibitor bevacizumab compared with bevacizumab monotherapy was reported in the Phase 3 PAOLA-1 study for patients with newly diagnosed advanced ovarian cancer in the intent-to-treat population (PFS: 22.1 vs. 16.6 months), the BRCA1/2-mutated population (PFS: 37.2 vs. 21.7 months), and the BRCA1/2-wildtype population harboring homologous recombination deficiency (HRD)-positive status (PFS: 28.1 vs. 16.6 months)[303]. For patients with platinum-sensitive recurrent ovarian cancer who previously progressed on chemotherapy, statistically increased median PFS was reported in a Phase 2 study of olaparib in combination with chemotherapy (PFS: 12.2 months) compared with chemotherapy alone (PFS: 9.6 months)[296], as well as from treatment with the VEGFR inhibitor cediranib compared with olaparib monotherapy in a Phase 1/2 trial[304]. The Phase 2 CAPRI study for PARP inhibitor-resistant patients with HRD, platinum-sensitive, high-grade ovarian cancer treated with

combination therapy of olaparib and the ATR inhibitor ceralasertib reported an ORR of 46% (n=13, 6 PRs) and a PFS of 7.5 months[305]. For patients with PARP-resistant ovarian cancer, the combination of olaparib and the WEE1-inhibitor adavosertib elicited improved clinical benefit (ORR: 29%; DCR: 89%) compared to adavosertib alone (ORR: 23%; DCR: 63%); however, in the BRCA-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR: 19%) and monotherapy (ORR: 20%) treatments[86].

Rucaparib

Assay findings association

BRCA2
S780*

Loss of Heterozygosity score
21.8%

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,283] . 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%[2,283] . On the basis of strong clinical evidence in ovarian cancer[2,68,214] , as well as clinical data in other cancer types[68,306-307] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib.

SUPPORTING DATA

The Phase 3 ARIEL4 trial of rucaparib for heavily pretreated patients with BRCA1- or BRCA2-mutated ovarian carcinoma reported improved median PFS (mPFS) for the rucaparib group compared with the chemotherapy-treated group (7.4 vs. 5.7 months, HR=0.64); for patients with BRCA reversion mutations, longer mPFS was reported following chemotherapy compared with rucaparib treatment (5.5 vs. 2.9 months, HR=2.77)[308]. In the Phase 3 ARIEL 3 study, rucaparib as maintenance therapy significantly improved mPFS (16.6 vs. 5.4 months, HR=0.23) with CR rates of 18% for patients with germline or somatic BRCA-mutated recurrent ovarian cancer compared with placebo treatment[1]. In the Phase 2 ARIEL 2 trial, patients with BRCA-mutated platinum-sensitive recurrent ovarian cancer experienced an mPFS of 12.8 months on rucaparib[2]. In the Phase 3 ATHENA study, rucaparib monotherapy significantly improved median PFS (mPFS) as first-line maintenance therapy compared with placebo for patients with ovarian cancer in both the homologous recombination deficient (HRD)-positive population (BRCA-mutated or BRCA-wildtype and high genomic loss of heterozygosity [LOH] score defined as ≥16%; mPFS of 28.7 vs. 11.3 months, HR=0.47) and the overall population (mPFS of 20.2 vs. 9.2 months, HR=0.52); exploratory subgroup analysis also reported benefit for the HRD-negative group (BRCA-wildtype and low genomic LOH score defined as <16%; mPFS of 12.1 vs. 9.1 months, HR=0.65)[309]. In the Phase 3 ARIEL3 study of rucaparib maintenance treatment for patients with platinum-sensitive high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, mPFS was significantly improved with rucaparib compared with placebo for patients, irrespective of HRD status or BRCA status, with benefit observed for both the LOH-high subgroup (13.6 vs. 5.4 months, HR=0.32) and the overall population (10.8 vs. 5.4 months, HR=0.36), with CR rates of 12% for the HRD-positive group and 7% for the overall population; PFS benefit was also observed for the BRCA-wildtype, LOH-low group (HR=0.58)[1]. In the Phase 2 ARIEL2 trial for patients with recurrent platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, mPFS on rucaparib was 5.7 months for patients with high LOH and 5.2 months for patients with low LOH[2].

Talazoparib

Assay findings association

BRCA2
S780*

Loss of Heterozygosity score
21.8%

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors[1-2,283] . 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%[2,283] . On the basis of strong clinical data in breast cancer[310-312] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[313-316] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

SUPPORTING DATA

An ORR of 42% (5/12) and median PFS of 36.4 weeks was reported for patients with BRCA1/2-mutated ovarian cancer treated with talazoparib in a Phase 1 study[314]. An ORR of 42% (5/12) was reported for patients with BRCA1/2-mutated ovarian cancer treated with talazoparib in a Phase 1 study[314]. In a Phase 2 study of talazoparib in advanced solid tumors, 1 patient with BRIP1-mutated ovarian carcinoma with wildtype BRCA status experienced a prolonged SD[317].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

BIOMARKER

Loss of Heterozygosity score

RATIONALE

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

RESULT

21.8%

NCT04729387

PHASE 3

Alpelisib Plus Olaparib in Platinum-resistant/Refractory, High-grade Serous Ovarian Cancer, With no Germline BRCA Mutation Detected

TARGETS
PARP, PI3K-alpha

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Shanghai (China), Wuhan (China), Jinan (China), Seoul (Korea, Republic of), Tianjin (China), Beijing (China), Kota Kinabalu (Malaysia), Kuching (Malaysia)

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: Hangzhou (China), Shanghai (China), Nantong (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China), Wuhan (China), Bengbu (China), Zhengzhou (China)

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Shanghai (China), Seoul (Korea, Republic of), Chongqing (China), Chuo-ku (Japan), Koto-ku (Japan), Melbourne (Australia), Warszawa (Poland), Gdynia (Poland), Grzepnica (Poland), Budapest (Hungary)

NCT04517357

PHASE 2

A Phase 2 Trial of Fluzoparib Combined With Apatinib Versus Fluzoparib Monotherapy in Treatment With Relapsed Ovarian Cancer Patients

TARGETS
RET, VEGFR2, PARP

LOCATIONS: Hangzhou (China)

NCT03983226

PHASE 2

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

TARGETS
PARP

LOCATIONS: Shanghai (China)

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NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04284852

PHASE 2

Niraparib Maintenance in Patients With Advanced Ovarian Cancer at Neoadjuvant Setting

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT04556071

PHASE 2

Efficacy and Safety of Niraparib Combined With Bevacizumab in Platinum Refractory/Resistant Recurrent Ovarian Cancer

TARGETS
VEGFA, PARP

LOCATIONS: Nanjing (China)

NCT04566952

PHASE 2

Anlotinib Combined With Dose-reduced Olaparib in Patients With Platinum-Sensitive Recurrent Ovarian Cancer

TARGETS
FGFRs, KIT, VEGFRs, PARP

LOCATIONS: Nanjing (China)

NCT04376073

PHASE 2

Anlotinib and Niraparib Dual Therapy Evaluation in Platinum-resistant Recurrent Ovarian Cancer

TARGETS
FGFRs, KIT, VEGFRs, PARP

LOCATIONS: Guangzhou (China)

GENE
BRCA2

ALTERATION
S780*

RATIONALE
BRCA2 loss or inactivating alterations may predict sensitivity to PARP inhibitors or to ATR inhibitors.

NCT04729387

PHASE 3

Alpelisib Plus Olaparib in Platinum-resistant/Refractory, High-grade Serous Ovarian Cancer, With no Germline BRCA Mutation Detected

TARGETS
PARP, PI3K-alpha

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Shanghai (China), Wuhan (China), Jinan (China), Seoul (Korea, Republic of), Tianjin (China), Beijing (China), Kota Kinabalu (Malaysia), Kuching (Malaysia)

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: Hangzhou (China), Shanghai (China), Nantong (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China), Wuhan (China), Bengbu (China), Zhengzhou (China)

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Shanghai (China), Seoul (Korea, Republic of), Chongqing (China), Chuo-ku (Japan), Koto-ku (Japan), Melbourne (Australia), Warszawa (Poland), Gdynia (Poland), Grzepnica (Poland), Budapest (Hungary)

NCT04517357

PHASE 2

A Phase 2 Trial of Fluzoparib Combined With Apatinib Versus Fluzoparib Monotherapy in Treatment With Relapsed Ovarian Cancer Patients

TARGETS
RET, VEGFR2, PARP

LOCATIONS: Hangzhou (China)

NCT03983226

PHASE 2

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

TARGETS
PARP

LOCATIONS: Shanghai (China)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

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NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04284852

PHASE 2

Niraparib Maintenance in Patients With Advanced Ovarian Cancer at Neoadjuvant Setting

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT04556071

PHASE 2

Efficacy and Safety of Niraparib Combined With Bevacizumab in Platinum Refractory/Resistant Recurrent Ovarian Cancer

TARGETS
VEGFA, PARP

LOCATIONS: Nanjing (China)

NCT04566952

PHASE 2

Anlotinib Combined With Dose-reduced Olaparib in Patients With Platinum-Sensitive Recurrent Ovarian Cancer

TARGETS
FGFRs, KIT, VEGFRs, PARP

LOCATIONS: Nanjing (China)

GENE
MYC

ALTERATION
amplification - equivocal

RATIONALE
MYC overexpression may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, including Aurora kinase A and B, and of BET domain proteins, which are reported to downregulate MYC expression and MYC-dependent transcriptional programs.

NCT04983810

PHASE 1/2

A Study to Investigate Fadraciclib (CYC065), in Subjects With Advanced Solid Tumors and Lymphoma

TARGETS
CDK2, CDK9

LOCATIONS: Seoul (Korea, Republic of), Barcelona (Spain), California, Texas

NCT04742959

PHASE 1/2

Crossover Relative Bioavailability and Dose Escalation Study of TT-00420 Tablet in Patients With Advanced Solid Tumors

TARGETS
Aurora kinase A, Aurora kinase B

LOCATIONS: California, Illinois, Ohio, Texas, New Jersey

NCT04553133

PHASE 2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS
CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Michigan, Massachusetts, Texas

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK9, CDK5, CDK2

LOCATIONS: Massachusetts

NCT04555837

PHASE 1/2

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

TARGETS
Aurora kinase A, PD-1

LOCATIONS: Texas

GENE
NF2

ALTERATION
E90fs*9

RATIONALE
Inactivation or loss of NF2 results in the dysregulation of mTOR and FAK pathway signaling. Therefore, mTOR and/or FAK inhibitors may be relevant for patients with NF2 inactivating mutations.

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT04625270

PHASE 2

A Study of VS-6766 v. VS-6766 + Defactinib in Recurrent Low-Grade Serous Ovarian Cancer With and Without a KRAS Mutation

TARGETS
RAFs, MEK, FAK

LOCATIONS: Liège (Belgium), Leuven (Belgium), Gent (Belgium), Edinburgh (United Kingdom), Milano (Italy), Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Paris (France)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03287271

PHASE 1/2

ROCKIF Trial: Re-sensitization of Carboplatin-resistant Ovarian Cancer With Kinase Inhibition of FAK

TARGETS
FAK

LOCATIONS: California

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

NCT03875820

PHASE 1

Phase I Trial of VS-6063 and RO5126766.

TARGETS
RAFs, MEK, FAK

LOCATIONS: Newcastle (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom)

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

GENE
TP53

ALTERATION
R156P

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

NCT04516447

PHASE 1

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

TARGETS
WEE1

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Nedlands (Australia), Sunshine Coast (Australia), South Brisbane (Australia), Melbourne (Australia), Panagyurishte (Bulgaria), Belgrade (Serbia), Tuzla (Bosnia and Herzegovina), Sarajevo (Bosnia and Herzegovina)

NCT03968653

PHASE 1

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

TARGETS
WEE1

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

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

FANCA I525V	***FANCG*** T568A	***FGF6*** L183M	***JAK3*** splice site 181_184+13del17
MSH6 A940S	***NKX2-1*** G322S	***RAD21*** amplification	***TBX3*** A562V

Electronically signed by Erik Williams, M.D. | 23 August 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV1*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*
KMT2A (MLL)	*MSH2*	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*
RAF1	*RARA*	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***
TMPRSS2								

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT

CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version 7.0.0

The median exon coverage for this sample is 950x

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1. Coleman RL, et al. Lancet (2017) pmid: 28916367
2. Swisher EM, et al. Lancet Oncol. (2017) pmid: 27908594
3. Mirza MR, et al. N. Engl. J. Med. (2016) pmid: 27717299
4. Telli ML, et al. Clin. Cancer Res. (2016) pmid: 26957554
5. Timms KM, et al. Breast Cancer Res. (2014) pmid: 25475740
6. Wang ZC, et al. Clin. Cancer Res. (2012) pmid: 22912389
7. Telli ML, et al. J. Clin. Oncol. (2015) pmid: 25847929
8. Isakoff SJ, et al. J. Clin. Oncol. (2015) pmid: 25847936
9. Elvin et al., 2017; ASCO Abstract 5512
10. Abkevich V, et al. Br. J. Cancer (2012) pmid: 23047548
11. Marquard AM, et al. Biomark Res (2015) pmid: 26015868
12. Pedersen BS, et al. Genes Chromosomes Cancer (2013) pmid: 23716468
13. Watkins JA, et al. Breast Cancer Res. (2014) pmid: 25093514
14. Vanderstichele A, et al. Eur. J. Cancer (2017) pmid: 28950147
15. Nature (2011) pmid: 21720365
16. N. Engl. J. Med. (2003) pmid: 12736286
17. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
18. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
19. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
20. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
21. Ayers et al., 2016; ASCO-SITC Abstract P60
22. Segev Y, et al. Eur. J. Gynaecol. Oncol. (2015) pmid: 26775351
23. Plisiecka-Hałasa J, et al. Anticancer Res. () pmid: 18507046
24. Huang HN, et al. Histopathology (2015) pmid: 25195947
25. Strickland et al., 2016; ASCO Abstract 5514
26. Aysal A, et al. Am. J. Surg. Pathol. (2012) pmid: 22189970
27. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
28. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
29. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
30. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
31. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
32. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
33. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
34. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
35. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
36. Cristescu R, et al. Science (2018) pmid: 30309915
37. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
38. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
39. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
40. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
41. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
42. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
43. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
44. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
45. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
46. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
47. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
48. Schenker at al., 2022; AACR Abstract 7845
49. Legrand et al., 2018; ASCO Abstract 12000
50. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
51. Strickland KC, et al. Oncotarget (2016) pmid: 26871470
52. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
53. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
54. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
55. Rizvi NA, et al. Science (2015) pmid: 25765070
56. Johnson BE, et al. Science (2014) pmid: 24336570
57. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
58. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
59. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
60. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
61. Nature (2012) pmid: 22810696
62. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
63. Kaufman B, et al. J. Clin. Oncol. (2015) pmid: 25366685
64. Mateo J, et al. N. Engl. J. Med. (2015) pmid: 26510020
65. Tutt A, et al. Lancet (2010) pmid: 20609467
66. Robson M, et al. N. Engl. J. Med. (2017) pmid: 28578601
67. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
68. Drew Y, et al. Br. J. Cancer (2016) pmid: 27002934
69. Pujade-Lauraine E, et al. Lancet Oncol. (2017) pmid: 28754483
70. Ledermann JA, et al. Lancet Oncol. (2016) pmid: 27617661
71. Fong PC, et al. N. Engl. J. Med. (2009) pmid: 19553641
72. Audeh MW, et al. Lancet (2010) pmid: 20609468
73. Fong PC, et al. J. Clin. Oncol. (2010) pmid: 20406929
74. Gelmon KA, et al. Lancet Oncol. (2011) pmid: 21862407
75. Kaye SB, et al. J. Clin. Oncol. (2012) pmid: 22203755
76. Domchek SM, et al. Gynecol. Oncol. (2016) pmid: 26723501
77. Moore K, et al. N. Engl. J. Med. (2018) pmid: 30345884
78. Golan T, et al. N. Engl. J. Med. (2019) pmid: 31157963
79. Yap TA, et al. Cancer Discov (2021) pmid: 32988960
80. Thomas A, et al. J. Clin. Oncol. (2018) pmid: 29252124
81. Saito YD, et al. Cancer Treat Res Commun (2018) pmid: 31299005
82. Pouliot GP, et al. PLoS ONE (2019) pmid: 31721781
83. Kim H, et al. Clin. Cancer Res. (2017) pmid: 27993965
84. Jin J, et al. Neoplasia (2018) pmid: 29605721
85. Coleman RL, et al. N. Engl. J. Med. (2019) pmid: 31562800
86. Westin et al., 2021; ASCO Abstract 5505
87. Do K, et al. J. Clin. Oncol. (2015) pmid: 25964244
88. Dann RB, et al. Gynecol. Oncol. (2012) pmid: 22406760
89. Evers B, et al. Clin. Cancer Res. (2008) pmid: 18559613
90. Soares DG, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17656556
91. Miolo G, et al. Cancer Biol. Ther. (2016) pmid: 27561088
92. Ghouadni A, et al. Breast (2017) pmid: 28467918
93. Case Rep Oncol () pmid: 28626402
94. Monk BJ, et al. Gynecol. Oncol. (2020) pmid: 31924332
95. Harnicek D, et al. Int. J. Cancer (2016) pmid: 26933761
96. Cruz C, et al. J. Clin. Oncol. (2018) pmid: 30240327
97. Poveda A, et al. Ann. Oncol. (2017) pmid: 28368437
98. Pennington KP, et al. Clin. Cancer Res. (2014) pmid: 24240112
99. Witjes VM, et al. Gynecol Oncol (2022) pmid: 34702566
100. Zhong Q, et al. Clin. Cancer Res. (2015) pmid: 25348513
101. Labidi-Galy SI, et al. Clin. Cancer Res. (2018) pmid: 29084914
102. Yang H, et al. Science (2002) pmid: 12228710
103. Nat. Struct. Mol. Biol. (2011) pmid: 21731065
104. Biswas K, et al. Blood (2011) pmid: 21719596
105. Biswas K, et al. Hum. Mol. Genet. (2012) pmid: 22678057
106. Claes K, et al. Br. J. Cancer (2004) pmid: 15026808
107. Cote S, et al. Breast Cancer Res. Treat. (2012) pmid: 21947752
108. Fackenthal JD, et al. Am. J. Hum. Genet. (2002) pmid: 12145750
109. Farrugia DJ, et al. Cancer Res. (2008) pmid: 18451181
110. Gómez García EB, et al. Breast Cancer Res. (2009) pmid: 19200354
111. Guidugli L, et al. Cancer Res. (2013) pmid: 23108138
112. Kluska A, et al. BMC Med Genomics (2015) pmid: 25948282
113. Kuznetsov SG, et al. Nat. Med. (2008) pmid: 18607349
114. Roy R, et al. Nat. Rev. Cancer (2011) pmid: 22193408
115. Siaud N, et al. PLoS Genet. (2011) pmid: 22194698
116. Thomassen M, et al. Genet. Test. (2006) pmid: 16792514
117. Xia B, et al. Mol. Cell (2006) pmid: 16793542
118. Guidugli L, et al. Am. J. Hum. Genet. (2018) pmid: 29394989
119. Fraile-Bethencourt E, et al. PLoS Genet. (2017) pmid: 28339459
120. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
121. Miki Y, et al. Science (1994) pmid: 7545954
122. Wooster R, et al. Nature () pmid: 8524414
123. King MC, et al. Science (2003) pmid: 14576434
124. MedGenMed (2005) pmid: 16369438
125. Ford D, et al. Lancet (1994) pmid: 7907678
126. Whittemore AS, et al. Am. J. Hum. Genet. (1997) pmid: 9042908
127. Claus EB, et al. Cancer (1996) pmid: 8635102
128. Struewing JP, et al. N. Engl. J. Med. (1997) pmid: 9145676
129. Oddoux C, et al. Nat. Genet. (1996) pmid: 8841192
130. Hall MJ, et al. Cancer (2009) pmid: 19241424
131. Horiuchi D, et al. J. Exp. Med. (2012) pmid: 22430491
132. Goga A, et al. Nat. Med. (2007) pmid: 17589519
133. Molenaar JJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19525400
134. Dammert MA, et al. Nat Commun (2019) pmid: 31375684
135. Mollaoglu G, et al. Cancer Cell (2017) pmid: 28089889
136. Cardnell RJ, et al. Oncotarget (2017) pmid: 29088717
137. Wang L, et al. Mol Oncol (2017) pmid: 28417568
138. Takahashi Y, et al. Ann. Oncol. (2015) pmid: 25632068
139. Li Y, et al. Thyroid (2018) pmid: 30226440
140. Mahadevan D, et al. PLoS ONE (2014) pmid: 24893165
141. Park SI, et al. Target Oncol (2019) pmid: 31429028
142. Helfrich BA, et al. Mol. Cancer Ther. (2016) pmid: 27496133
143. Hook KE, et al. Mol. Cancer Ther. (2012) pmid: 22222631
144. Yang D, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20643922
145. He J, et al. Anticancer Drugs (2019) pmid: 30540594
146. Shroff EH, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25964345
147. Effenberger M, et al. Oncotarget (2017) pmid: 29156762
148. Qu X, et al. Biochem. Biophys. Res. Commun. (2018) pmid: 30103944
149. Xiang Y, et al. J. Clin. Invest. (2015) pmid: 25915584

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150. Delmore JE, et al. Cell (2011) pmid: 21889194
151. Bandopadhayay P, et al. Clin. Cancer Res. (2014) pmid: 24297863
152. Lovén J, et al. Cell (2013) pmid: 23582323
153. Otto C, et al. Neoplasia (2019) pmid: 31734632
154. Dong LH, et al. J Hematol Oncol (2013) pmid: 23866964
155. Pei Y, et al. Cancer Cell (2016) pmid: 26977882
156. Fu XH, et al. Acta Pharmacol. Sin. (2019) pmid: 30224636
157. Owonikoko TK, et al. J Thorac Oncol (2020) pmid: 31655296
158. Ganesan P, et al. Mol. Cancer Ther. (2014) pmid: 25253784
159. Pereira CB, et al. PLoS ONE (2013) pmid: 23555992
160. Yasojima H, et al. Eur. J. Cancer (2011) pmid: 21741827
161. Arango D, et al. Cancer Res. (2001) pmid: 11406570
162. Bottone MG, et al. Exp. Cell Res. (2003) pmid: 14516787
163. Prathapam T, et al. J. Biol. Chem. (2010) pmid: 20647308
164. Koboldt DC, et al. Genome Res. (2012) pmid: 22300766
165. Sasano H, et al. Hum. Pathol. (1990) pmid: 1969381
166. Dimova I, et al. Eur. J. Cancer (2006) pmid: 16458500
167. Chen CH, et al. Int. J. Gynecol. Cancer () pmid: 16174239
168. Katsaros D, et al. Anticancer Res. () pmid: 7654038
169. Dang CV, et al. Semin. Cancer Biol. (2006) pmid: 16904903
170. Nesbit CE, et al. Oncogene (1999) pmid: 10378696
171. Blancato J, et al. Br. J. Cancer (2004) pmid: 15083194
172. Fromont G, et al. Hum. Pathol. (2013) pmid: 23574779
173. López-Lago MA, et al. Mol. Cell. Biol. (2009) pmid: 19451229
174. James MF, et al. Mol. Cell. Biol. (2009) pmid: 19451225
175. Pachow D, et al. Clin. Cancer Res. (2013) pmid: 23406776
176. Iyer G, et al. Science (2012) pmid: 22923433
177. Ali SM, et al. Eur. Urol. (2015) pmid: 25630452
178. Moulder S, et al. Ann. Oncol. (2015) pmid: 25878190
179. Soria JC, et al. Ann. Oncol. (2016) pmid: 27733373
180. Brastianos et al., 2020; ASCO Abstract 2502
181. Poulikakos PI, et al. Oncogene (2006) pmid: 16652148
182. Shapiro IM, et al. Sci Transl Med (2014) pmid: 24848258
183. Shah NR, et al. Gynecol. Oncol. (2014) pmid: 24786638
184. Ammoun S, et al. Neuro-oncology (2010) pmid: 20511180
185. Karajannis MA, et al. Neuro-oncology (2012) pmid: 22844108
186. Subbiah et al., 2011; ASCO Abstract 2100
187. Garcia-Rendueles ME, et al. Cancer Discov (2015) pmid: 26359368
188. Ammoun S, et al. Cancer Res. (2008) pmid: 18593924
189. Yi C, et al. Cancer Cell (2011) pmid: 21481793
190. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
191. Patterson et al., 2018; AACR Abstract 3891
192. Curto M, et al. Br. J. Cancer (2008) pmid: 17971776
193. Laulajainen M, et al. J. Cell. Mol. Med. (2012) pmid: 22325036
194. Lallemand D, et al. J. Cell. Sci. (2009) pmid: 19910496
195. Sherman L, et al. Oncogene (1997) pmid: 9395247
196. Li W, et al. EMBO Rep. (2012) pmid: 22482125
197. Manetti ME, et al. Biol Open (2012) pmid: 23213372
198. Stokowski RP, et al. Am. J. Hum. Genet. (2000) pmid: 10712203
199. Mani T, et al. Mol. Cell. Biol. (2011) pmid: 21402777
200. Evans GR, et al. Adv. Otorhinolaryngol. (2011) pmid: 21358190
201. Lu-Emerson C, et al. Rev Neurol Dis (2009) pmid: 19898272
202. Asthagiri AR, et al. Lancet (2009) pmid: 19476995
203. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
204. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
205. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
206. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
207. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
208. Xu L, et al. Mol. Med. (2001) pmid: 11713371
209. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
210. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
211. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
212. Hajdenberg et al., 2012; ASCO Abstract e15010
213. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
214. Moore et al., 2019; ASCO Abstract 5513
215. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
216. Oza et al., 2015; ASCO Abstract 5506
217. Lee J, et al. Cancer Discov (2019) pmid: 31315834
218. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
219. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
220. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
221. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
222. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
223. Gourley et al., 2016; ASCO Abstract 5571
224. Kwok M, et al. Blood (2016) pmid: 26563132
225. Boudny M, et al. Haematologica (2019) pmid: 30975914
226. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
227. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
228. Ahmed AA, et al. J. Pathol. (2010) pmid: 20229506
229. Wojnarowicz PM, et al. PLoS ONE (2012) pmid: 23029043
230. Kuhn E, et al. J. Pathol. (2012) pmid: 21990067
231. Karst AM, et al. J Oncol (2010) pmid: 19746182
232. Gadducci A, et al. Gynecol. Endocrinol. (2012) pmid: 22304686
233. Rechsteiner M, et al. Exp. Mol. Pathol. (2013) pmid: 23965232
234. Okamoto A, et al. Cancer Res. (1991) pmid: 1680546
235. McConechy MK, et al. Mod. Pathol. (2014) pmid: 23765252
236. de Graeff P, et al. Br. J. Cancer (2009) pmid: 19513073
237. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
238. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
239. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
240. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
241. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
242. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
243. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
244. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
245. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
246. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
247. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
248. Lalloo F, et al. Lancet (2003) pmid: 12672316
249. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
250. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
251. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
252. Xie M, et al. Nat. Med. (2014) pmid: 25326804
253. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
254. Severson EA, et al. Blood (2018) pmid: 29678827
255. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
256. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
257. Chabon JJ, et al. Nature (2020) pmid: 32269342
258. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
259. Joly MO, et al. Hum. Mutat. (2015) pmid: 25504677
260. Pritchard CC, et al. Nat Commun (2014) pmid: 25255306
261. Rosty C, et al. Fam. Cancer (2014) pmid: 25117503
262. McConechy MK, et al. Gynecol. Oncol. (2015) pmid: 25636458
263. Le et al., 2015; ASCO Abstract LBA100
264. Lipson EJ, et al. Clin. Cancer Res. (2013) pmid: 23169436
265. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
266. Bonadona V, et al. JAMA (2011) pmid: 21642682
267. Li F, et al. Cell (2013) pmid: 23622243
268. Wu H, et al. PLoS ONE (2011) pmid: 21720545
269. Edelbrock MA, et al. Mutat. Res. () pmid: 23391514
270. Berends MJ, et al. Am. J. Hum. Genet. (2002) pmid: 11709755
271. Warren JJ, et al. Mol. Cell (2007) pmid: 17531815
272. Geng H, et al. J. Biol. Chem. (2012) pmid: 22277660
273. Silva FC, et al. Sao Paulo Med J (2009) pmid: 19466295
274. Raevaara TE, et al. Gastroenterology (2005) pmid: 16083711
275. Kastrinos F, et al. Semin. Oncol. (2007) pmid: 17920897
276. Sehgal R, et al. Genes (Basel) (2014) pmid: 24978665
277. Fam. Cancer (2005) pmid: 16136383
278. Wimmer K, et al. Hum. Genet. (2008) pmid: 18709565
279. Wimmer K, et al. J. Med. Genet. (2014) pmid: 24737826
280. Scott RH, et al. Nat Clin Pract Oncol (2007) pmid: 17259933
281. Ripperger T, et al. Haematologica (2010) pmid: 20015892
282. Baris HN, et al. Pediatr Blood Cancer (2016) pmid: 26544533
283. Coleman et al., 2016; ASCO Abstract 5540
284. Konstantinopolous et al., 2018; ASCO Abstract 106
285. Fabbro M, et al. Gynecol. Oncol. (2019) pmid: 30638768
286. González-Martín A, et al. N. Engl. J. Med. (2019) pmid: 31562799
287. Moore KN, et al. Lancet Oncol. (2019) pmid: 30948273
288. Mirza MR, et al. Lancet Oncol. (2019) pmid: 31474354
289. Konstantinopoulos PA, et al. JAMA Oncol (2019) pmid: 31194228
290. Del Conte G, et al. Br. J. Cancer (2014) pmid: 25025963
291. Penson RT, et al. J Clin Oncol (2020) pmid: 32073956
292. Penson et al., 2022; SGO Abstract 25
293. Lee JY, et al. J Gynecol Oncol (2022) pmid: 35320892
294. Drew et al., 2019; ESMO Abstract 1190PD
295. Ledermann J, et al. Lancet Oncol. (2014) pmid: 24882434
296. Oza AM, et al. Lancet Oncol. (2015) pmid: 25481791
297. Matulonis UA, et al. Ann. Oncol. (2016) pmid: 26961146
298. Maio et al., 2021; AACR Abstract CT178
299. Poveda et al., 2020; ASCO Abstract 6002
300. Ledermann J, et al. N. Engl. J. Med. (2012) pmid: 22452356
301. Banerjee et al., 2020; ESMO Abstract 811MO

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302. Pujade-Lauraine et al., 2021; ESMO Abstract LBA33
303. Ray-Coquard et al., 2019; ESMO Abstract LBA2
304. Liu JF, et al. Lancet Oncol. (2014) pmid: 25218906
305. Wethington et al., 2021; ASCO Abstract 5516
306. Kristeleit et al., 2014; ASCO Abstract 2573
307. Domcheck et al., 2016; ASCO Abstract 4110
308. Kristeleit R, et al. Lancet Oncol (2022) pmid: 35298906
309. Monk et al., 2022; ASCO Abstract LBA5500
310. Turner et al., 2017; ASCO Abstract 1007
311. Litton JK, et al. N. Engl. J. Med. (2018) pmid: 30110579
312. Ettl J, et al. Ann. Oncol. (2018) pmid: 30124753
313. Meehan et al., 2017; AACR Abstract 4687
314. de Bono J, et al. Cancer Discov (2017) pmid: 28242752
315. Lu E, et al. J Natl Compr Canc Netw (2018) pmid: 30099369
316. De Bono et al., 2020; ASCO Abstract 5566
317. Piha Paul et al., 2018; AACR abstract A096

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