FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chen, Su Ping	Ovary clear cell carcinoma	21 Mar 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1587798-01

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 clear cell carcinoma
NAME Chen, Su Ping
DATE OF BIRTH 06 February 1971
SEX Female
MEDICAL RECORD # 30431324

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 Ovary
SPECIMEN ID S112-65411 H (PF23029)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 06 February 2023
SPECIMEN RECEIVED 15 March 2023

Biomarker Findings

Homologous Recombination status - HRD Not Detected
Loss of Heterozygosity score - 4.4%
Microsatellite status - MS-Stable
Tumor Mutational Burden - 5 Muts/Mb

Genomic Findings

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

ARID1A P729fs*15
MYC amplification - equivocal†
ABL1 R589C
ERBB3 amplification - equivocal†

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

† See About the Test in appendix for details.

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 7)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Homologous Recombination status - HRD Not Detected	HRD Not Detected defined as absence of deleterious *BRCA1/2* alteration and LOH score < 16% or Cannot Be Determined (Coleman et al., 2017; 28916367).
Loss of Heterozygosity score - 4.4%	**No therapies or clinical trials.** See Biomarker Findings section
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 5 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
***ARID1A* -** P729fs*15	none	none
10 Trials see p. 7		
***MYC* -** amplification - equivocal	none	none
10 Trials see p. 9		

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.

ABL1 - R589C .... p. 6

ERBB3 - amplification - equivocal .... p. 6

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

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

BIOMARKER

Loss of Heterozygosity score

RESULT
4.4%

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 below levels that have been associated with improved rates of clinical benefit from treatment with the PARP inhibitor rucaparib in patients with platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma[2]. However, patients with lower genomic LOH have also responded to rucaparib, and this type of LOH score does not preclude benefit from PARP inhibitors[1-2].

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].

BIOMARKER

Tumor Mutational Burden

RESULT
5 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 clear cell carcinoma harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 1.7% 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].

GENE
ARID1A

ALTERATION
P729fs*15

TRANSCRIPT ID
NM_006015.4

CODING SEQUENCE EFFECT
2185_2186insTGGGC

VARIANT CHROMOSOMAL POSITION
chr1:27087897

VARIANT ALLELE FREQUENCY (% VAF)
35.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[63]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[64]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[65]. In a Phase 1 trial, a patient with metastatic colorectal cancer (CRC) harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[66]. On the basis of limited clinical and preclinical evidence, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[67-68]. A Phase 1 study of EZH2 inhibitor CPI-0209 reported 1 PR for a patient with ARID1A-mutated endometrial cancer[69]. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[70-72]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[73]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[74-75] and to 5-fluorouracil in CRC cell lines[76].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2023)[77-85]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[24,73,86-88], CRC[73,89-91], and gastric cancer[73,92-96]. Several studies have reported no correlation between ARID1A loss and clinicopathological parameters in ovarian clear cell or endometrioid carcinomas or other endometrial cancers[97-100], whereas others suggest that ARID1A loss is a negative prognostic factor[75,101].

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[81,95,102-108]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[81,93,103-104,109], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
MYC

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited clinical data indicates that MYC activation may predict sensitivity to the pan-MYC inhibitor OMO-103; a Phase 1 study for patients with solid tumors reported 7 SDs (n=18), including 8% tumor reduction in a patient with pancreas adenocarcinoma[110]. Preclinical data indicate MYC overexpression may predict sensitivity to investigational agents targeting CDK1[111-112], CDK2[113], Aurora kinase A[114-121], Aurora kinase B[122-125], glutaminase[126-129], or BET bromodomain-containing proteins[130-133], as well as agents targeting both HDAC and PI3K[134-136]. 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[137]. A PR was reported for a patient with MYC-amplified invasive ductal breast carcinoma treated with an unspecified Aurora kinase inhibitor and taxol[138].

— Nontargeted Approaches —

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[139-140]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[141-142].

FREQUENCY & PROGNOSIS

Amplification of the MYC gene has been identified in 25-60% of ovarian tumors[15,143-146]. Overexpression of the MYC protein has been observed in 66% (31/47) of ovarian epithelial tumors[147]. For patients with ovarian carcinoma, MYC amplification has been associated with increased malignancy, higher histological grade, and poorer OS[146,148].

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[149]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[150]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[149,151-152].

GENE

ABL1

ALTERATION
R589C

TRANSCRIPT ID
NM_005157.4

CODING SEQUENCE EFFECT
1765C>T

VARIANT CHROMOSOMAL POSITION
chr9:133759442

VARIANT ALLELE FREQUENCY (% VAF)
64.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The BCR-ABL fusion protein is the best studied ABL1 alteration and exhibits increased ABL kinase activity; therapies to inhibit activated ABL1 have focused on BCR-ABL-positive hematological malignancies[153-154]. Activating fusions involving ABL1 may be sensitive to ABL inhibitors such as nilotinib, dasatinib, ponatinib, bosutinib, and imatinib[155-159]. Missense mutations occurring in the BCR-ABL1 kinase domain may contribute to resistance to ABL1 inhibitors[157]. However, the clinical utility of such therapies in solid tumors is unclear.

FREQUENCY & PROGNOSIS

ABL1 mutations have been reported in 0.4-4.0% of colorectal adenocarcinomas (CRC)[61,160-161], 3.2% of uterine corpus endometrial carcinomas[58], 2.4% of stomach adenocarcinomas[162], 1.7% of lung squamous cell carcinomas[163], and less than 1% of lung adenocarcinoma cases[164]. The prognostic significance of ABL1 alterations in the context of solid tumors is unknown (PubMed, Feb 2023)[165].

FINDING SUMMARY

ABL1 encodes the Abelson tyrosine protein kinase 1, which is involved in regulating cell growth, motility, and survival[165-167]. ABL1 kinase activation has been reported in several tumor types[165,168-169]. Although activating ABL1 fusions and resistance mutations have been reported in hematological malignancies[157,170], the role of ABL1 alterations in solid tumors is unclear[165,171].

GENE

ERBB3

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

ERBB3 cooperates with other ERBB family members, in particular ERBB2, for efficient signaling[172-175]. Therefore, ERBB3 amplification or activating mutation may predict sensitivity to therapies targeting ERBB2, including antibodies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), and dual EGFR/HER2 TKIs such as lapatinib and afatinib. Clinical and preclinical data support sensitivity of ERBB3 activating mutations to various anti-ERBB2 agents[174,176-180], but data are generally limited for ERBB3 amplification. Biomarker analyses of several Phase 3 trials have not identified an association of ERBB3 expression levels with benefit from trastuzumab-, pertuzumab-, or T-DM1-containing regimens in HER2-positive breast cancer[181-184], T-DM1 in HER2-positive gastric and gastroesophageal junction (GEJ) cancer[185], pertuzumab combined with chemotherapy in ovarian cancer[186], or afatinib in HNSCC[187]. Similarly, ERBB3 expression levels were not associated with PFS or OS from lapatinib plus capecitabine in a Phase 2 study of gastric/GEJ cancer[188] or in retrospective studies of HER2-positive breast cancer[189-191].

FREQUENCY & PROGNOSIS

In the Ovarian Serous Cystadenocarcinoma TCGA dataset, ERBB3 amplification and mutation were detected in 4% and <1% of cases, respectively[15]. In the literature, overexpression of ERBB3 protein has been detected in 53-76% of ovarian carcinomas[192-193]. ERBB3 protein overexpression in ovarian cancer has been correlated with poor prognosis[193-195].

FINDING SUMMARY

ERBB3 (also known as HER3) encodes a member of the epidermal growth factor receptor (EGFR) family[196]. One study has demonstrated a weak but significant association between ERBB3 gene amplification and ERBB3 protein expression in breast cancer tissue[197].

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.

GENE
ARID1A

ALTERATION
P729fs*15

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors. On the basis of preclinical evidence, ARID1A loss or inactivation may predict sensitivity to EZH2 and BET/BRD inhibitors.

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)

NCT04657068

PHASE 1/2

A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
ATR

LOCATIONS: London (United Kingdom), Colorado, Oklahoma, Texas, Pennsylvania, Tennessee, Florida

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Illinois, Texas, Georgia

NCT05053971

PHASE 1/2

Testing A New Anti-cancer Drug Combination, Entinostat and ZEN003694, for Advanced and Refractory Solid Tumors and Lymphomas

TARGETS
BRD3, BRD4, BRD2, BRDT, HDAC

LOCATIONS: Oklahoma, Connecticut, Florida

NCT05071937

PHASE 2

ZEN003694 Combined With Talazoparib in Patients With Recurrent Ovarian Cancer

TARGETS
BRD4, BRDT, BRD2, BRD3, PARP

LOCATIONS: Pennsylvania

NCT04266912

PHASE 1/2

Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors

TARGETS
ATR, PD-L1

LOCATIONS: Texas

NCT04104776

PHASE 1/2

A Study of CPI-0209 in Patients With Advanced Solid Tumors

TARGETS
EZH2, TOP1

LOCATIONS: Washington, Salamanca (Spain), Michigan, Illinois, Ohio, Massachusetts, New Jersey, New York

NCT04491942

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to the Usual Chemotherapy Treatment (Cisplatin, or Cisplatin and Gemcitabine) for Advanced Solid Tumors With Emphasis on Urothelial Cancer

TARGETS
ATR

LOCATIONS: California, Wisconsin, Toronto (Canada), Ohio, Pennsylvania, Maryland

NCT05252390

PHASE 1/2

NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors

TARGETS
BRD4, PARP, AR

LOCATIONS: Montana, California, Arizona, Michigan, Texas, Tennessee, Maryland, Virginia, North Carolina

NCT04514497

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
TOP1, ATR

LOCATIONS: Arizona, Minnesota, Oklahoma, Missouri, Pennsylvania, Connecticut, New York, Tennessee, Florida

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.

NCT04553133

PHASE 1/2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS
CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Shanghai (China), Koto (Japan), Kashiwa (Japan), Iowa, Michigan, Massachusetts, Kentucky, New York

NCT05253053

PHASE 1/2

Study to Evaluate the Efficacy and Safety of TT-00420 as Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors

TARGETS
Aurora kinase A, Aurora kinase B, PD-L1

LOCATIONS: Jinan (China), Beijing (China)

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

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Illinois, Texas, Georgia

NCT05053971

PHASE 1/2

Testing A New Anti-cancer Drug Combination, Entinostat and ZEN003694, for Advanced and Refractory Solid Tumors and Lymphomas

TARGETS
BRD3, BRD4, BRD2, BRDT, HDAC

LOCATIONS: Oklahoma, Connecticut, Florida

NCT05071937

PHASE 2

ZEN003694 Combined With Talazoparib in Patients With Recurrent Ovarian Cancer

TARGETS
BRD4, BRDT, BRD2, BRD3, PARP

LOCATIONS: Pennsylvania

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

NCT05252390

PHASE 1/2

NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors

TARGETS
BRD4, PARP, AR

LOCATIONS: Montana, California, Arizona, Michigan, Texas, Tennessee, Maryland, Virginia, North Carolina

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

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK9, CDK5, CDK2

LOCATIONS: Massachusetts

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.

ARFRP1 amplification	***ASXL1*** amplification	***AURKA*** amplification	***BCL2L1*** amplification
BCORL1 V872G	***ERRFI1*** P347S	***GNAS*** amplification	***KDM5A*** T269N
LYN amplification	***MET*** E868K	***NBN*** amplification	***NOTCH3*** S696I
PIK3C2G D8Y	***PRDM1*** I573M	***RAD21*** amplification	***SDHB*** A271S
SRC amplification	***TSC2*** T1330M	***WHSC1 (MMSET)*** S102T	***ZNF217*** amplification

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLE

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

Using an Illumina® 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. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

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

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out 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 (RG) 7.6.0

The median exon coverage for this sample is 973x

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. Williamson CT, et al. Nat Commun (2016) pmid: 27958275
64. Aggarwal et al., 2021; ESMO Abstract 512O
65. Thomas A, et al. J. Clin. Oncol. (2018) pmid: 29252124
66. Yap TA, et al. J Clin Oncol (2020) pmid: 32568634
67. Bitler BG, et al. Nat. Med. (2015) pmid: 25686104
68. Kim KH, et al. Nat. Med. (2015) pmid: 26552009
69. Papadopoulos et al., 2022; ENA Abstract 188
70. Wiegand KC, et al. BMC Cancer (2014) pmid: 24559118
71. Huang HN, et al. Mod. Pathol. (2014) pmid: 24336158
72. Samartzis EP, et al. Oncotarget (2014) pmid: 24979463
73. Okamura R, et al. J Immunother Cancer (2020) pmid: 32111729
74. Yokoyama Y, et al. J Gynecol Oncol (2014) pmid: 24459582
75. Katagiri A, et al. Mod. Pathol. (2012) pmid: 22101352
76. Xie C, et al. Tumour Biol. (2014) pmid: 24833095
77. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
78. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
79. Gao J, et al. Sci Signal (2013) pmid: 23550210
80. Wu RC, et al. Cancer Biol. Ther. (2014) pmid: 24618703
81. Jones S, et al. Hum. Mutat. (2012) pmid: 22009941
82. Dulak AM, et al. Nat. Genet. (2013) pmid: 23525077
83. Streppel MM, et al. Oncogene (2014) pmid: 23318448
84. Jiao Y, et al. J. Pathol. (2014) pmid: 24293293
85. Ross JS, et al. Oncologist (2014) pmid: 24563076
86. Hussein YR, et al. Mod. Pathol. (2015) pmid: 25394778
87. Bosse T, et al. Mod. Pathol. (2013) pmid: 23702729
88. Allo G, et al. Mod. Pathol. (2014) pmid: 23887303
89. Chou A, et al. Hum. Pathol. (2014) pmid: 24925223
90. Ye J, et al. Hum. Pathol. (2014) pmid: 25311944
91. Wei XL, et al. World J. Gastroenterol. (2014) pmid: 25561809
92. Chen K, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25583476
93. Wang K, et al. Nat. Genet. (2011) pmid: 22037554
94. Abe H, et al. Virchows Arch. (2012) pmid: 22915242
95. Wang DD, et al. PLoS ONE (2012) pmid: 22808142
96. Wiegand KC, et al. Hum. Pathol. (2014) pmid: 24767857
97. Rahman M, et al. Hum. Pathol. (2013) pmid: 22939958
98. Maeda D, et al. Int J Mol Sci (2010) pmid: 21614196
99. Lowery WJ, et al. Int. J. Gynecol. Cancer (2012) pmid: 22193641
100. Fadare O, et al. Mod. Pathol. (2013) pmid: 23524907
101. Mao TL, et al. Am. J. Surg. Pathol. (2013) pmid: 24076775
102. Guan B, et al. Cancer Res. (2011) pmid: 21900401
103. Wiegand KC, et al. N. Engl. J. Med. (2010) pmid: 20942669
104. Jones S, et al. Science (2010) pmid: 20826764
105. Yan HB, et al. Carcinogenesis (2014) pmid: 24293408
106. Huang J, et al. Nat. Genet. (2012) pmid: 22922871
107. Chan-On W, et al. Nat. Genet. (2013) pmid: 24185513
108. Mamo A, et al. Oncogene (2012) pmid: 21892209
109. Zang ZJ, et al. Nat. Genet. (2012) pmid: 22484628
110. Garralda et al., 2022; ENA Abstract 7
111. Horiuchi D, et al. J. Exp. Med. (2012) pmid: 22430491
112. Goga A, et al. Nat. Med. (2007) pmid: 17589519
113. Molenaar JJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19525400
114. Dammert MA, et al. Nat Commun (2019) pmid: 31375684
115. Mollaoglu G, et al. Cancer Cell (2017) pmid: 28089889
116. Cardnell RJ, et al. Oncotarget (2017) pmid: 29088717
117. Wang L, et al. Mol Oncol (2017) pmid: 28417568
118. Takahashi Y, et al. Ann. Oncol. (2015) pmid: 25632068
119. Li Y, et al. Thyroid (2018) pmid: 30226440
120. Mahadevan D, et al. PLoS ONE (2014) pmid: 24893165
121. Park SI, et al. Target Oncol (2019) pmid: 31429028
122. Helfrich BA, et al. Mol. Cancer Ther. (2016) pmid: 27496133
123. Hook KE, et al. Mol. Cancer Ther. (2012) pmid: 22222631
124. Yang D, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20643922
125. He J, et al. Anticancer Drugs (2019) pmid: 30540594
126. Shroff EH, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25964345
127. Effenberger M, et al. Oncotarget (2017) pmid: 29156762
128. Qu X, et al. Biochem. Biophys. Res. Commun. (2018) pmid: 30103944
129. Xiang Y, et al. J. Clin. Invest. (2015) pmid: 25915584
130. Delmore JE, et al. Cell (2011) pmid: 21889194
131. Bandopadhayay P, et al. Clin. Cancer Res. (2014) pmid: 24297863
132. Lovén J, et al. Cell (2013) pmid: 23582323
133. Otto C, et al. Neoplasia (2019) pmid: 31734632
134. Dong LH, et al. J Hematol Oncol (2013) pmid: 23866964
135. Pei Y, et al. Cancer Cell (2016) pmid: 26977882
136. Fu XH, et al. Acta Pharmacol. Sin. (2019) pmid: 30224636
137. Owonikoko TK, et al. J Thorac Oncol (2020) pmid: 31655296
138. Ganesan P, et al. Mol. Cancer Ther. (2014) pmid: 25253784
139. Pereira CB, et al. PLoS ONE (2013) pmid: 23555992
140. Yasojima H, et al. Eur. J. Cancer (2011) pmid: 21741827
141. Arango D, et al. Cancer Res. (2001) pmid: 11406570
142. Bottone MG, et al. Exp. Cell Res. (2003) pmid: 14516787
143. Prathapam T, et al. J. Biol. Chem. (2010) pmid: 20647308
144. Koboldt DC, et al. Genome Res. (2012) pmid: 22300766
145. Sasano H, et al. Hum. Pathol. (1990) pmid: 1969381
146. Dimova I, et al. Eur. J. Cancer (2006) pmid: 16458500
147. Chen CH, et al. Int. J. Gynecol. Cancer () pmid: 16174239
148. Katsaros D, et al. Anticancer Res. () pmid: 7654038
149. Dang CV, et al. Semin. Cancer Biol. (2006) pmid: 16904903
150. Nesbit CE, et al. Oncogene (1999) pmid: 10378696
151. Blancato J, et al. Br. J. Cancer (2004) pmid: 15083194
152. Fromont G, et al. Hum. Pathol. (2013) pmid: 23574779
153. Nat. Rev. Cancer (2005) pmid: 15719031

154. O'Hare T, et al. Nat. Rev. Cancer (2012) pmid: 22825216
155. Santos FP, et al. Curr Hematol Malig Rep (2011) pmid: 21327563
156. Reddy EP, et al. Genes Cancer (2012) pmid: 23226582
157. Soverini S, et al. Blood (2011) pmid: 21562040
158. Keller-V Amsberg G, et al. Expert Rev Anticancer Ther (2012) pmid: 23098112
159. Testoni E, et al. EMBO Mol Med (2016) pmid: 26758680
160. Seshagiri S, et al. Nature (2012) pmid: 22895193
161. Fumagalli D, et al. BMC Cancer (2010) pmid: 20233444
162. Nature (2014) pmid: 25079317
163. Nature (2012) pmid: 22960745
164. Nature (2014) pmid: 25079552
165. Greuber EK, et al. Nat. Rev. Cancer (2013) pmid: 23842646
166. Sci Signal (2010) pmid: 20841568
167. Bradley WD, et al. J. Cell. Sci. (2009) pmid: 19759284
168. Drake JM, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22307624
169. Cho NL, et al. Biochem. Biophys. Res. Commun. (2012) pmid: 22521882
170. Quintás-Cardama A, et al. Blood (2009) pmid: 18827185
171. Ganguly SS, et al. Genes Cancer (2012) pmid: 23226579
172. Black LE, et al. Am. J. Pathol. (2019) pmid: 31351986
173. Baselga J, et al. Nat. Rev. Cancer (2009) pmid: 19536107
174. Jaiswal BS, et al. Cancer Cell (2013) pmid: 23680147
175. Jura N, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 20007378
176. Choudhury NJ, et al. J. Clin. Oncol. (2016) pmid: 27044931
177. Verlingue L, et al. Eur. J. Cancer (2018) pmid: 29413684
178. Bidard FC, et al. Ann. Oncol. (2015) pmid: 25953157
179. Umelo I, et al. Oncotarget (2016) pmid: 26689995
180. Mishra R, et al. Oncotarget (2018) pmid: 29963236
181. Perez EA, et al. BMC Cancer (2019) pmid: 31146717
182. Baselga J, et al. J. Clin. Oncol. (2014) pmid: 25332247
183. Kim SB, et al. Int. J. Cancer (2016) pmid: 27428671
184. Baselga J, et al. Clin. Cancer Res. (2016) pmid: 26920887
185. Shah MA, et al. Gastric Cancer (2019) pmid: 30706247
186. Kurzeder C, et al. J. Clin. Oncol. (2016) pmid: 27269942
187. Cohen EEW, et al. Ann. Oncol. (2017) pmid: 28961833
188. LaBonte MJ, et al. Mol. Cancer Ther. (2016) pmid: 27325685
189. Nishimura R, et al. Oncology (2017) pmid: 28478451
190. Duchnowska R, et al. Oncotarget (2017) pmid: 29262628
191. Fabi A, et al. Expert Opin Pharmacother (2013) pmid: 23472669
192. Davies S, et al. Int. J. Gynecol. Pathol. (2014) pmid: 24901400
193. Tanner B, et al. J. Clin. Oncol. (2006) pmid: 16896008
194. Leng J, et al. Chin. Med. Sci. J. (1997) pmid: 11324501
195. Sithanandam G, et al. Cancer Gene Ther. (2008) pmid: 18404164
196. Sheng Q, et al. Br. J. Cancer (2011) pmid: 21364581
197. Sassen A, et al. Breast Cancer Res. (2008) pmid: 18182100