PATIENT	TUMOR TYPE		REPORT DATE
Kao, Chen Hsin	Ovary high grade serous carcinoma		10 Oct 2022
	COUNTRY CODE		ORDERED TEST #
	TW		ORD-1468925-01

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 high grade serous carcinoma
NAME Kao, Chen Hsin
DATE OF BIRTH 10 January 1940
SEX Female
MEDICAL RECORD # 21100345

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 S111-68367K (PF22111)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 20 September 2022
SPECIMEN RECEIVED 30 September 2022

Biomarker Findings
Loss of Heterozygosity score - 16.8%
Homologous Recombination status - HRD Positive
Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

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

MET amplification
TP53 S127P
CSF3R amplification
MYCL1 amplification
PRKCI amplification
TERC amplification

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

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. 15)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Loss of Heterozygosity score - 16.8%	Niraparib	2A	Talazoparib
	Olaparib	2A	
	Rucaparib	2A	
10 Trials see p. 15			
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 - 1 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section		

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carcinoma

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MET - amplification	none	Cabozantinib
		Capmatinib
		Crizotinib
6 Trials see p. 17		Tepotinib
TP53 - S127P	none	none
2 Trials see p. 19		

☐ *NCCN category*

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.

CSF3R - amplification	p. 7	*PRKCI -* amplification	p. 8
MYCL1 - amplification	p. 7	*TERC -* amplification	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.

Electronically signed by Erik Williams, M.D. | 10 October 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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PATIENT
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BIOMARKER FINDINGS

BIOMARKER
Loss of Heterozygosity score

RESULT
16.8%

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
1 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
MET

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[63-66], gastroesophageal cancer[67], glioblastoma[68], and carcinoma of unknown primary[69]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified cholangiocarcinoma[70], as well as MET-amplified NSCLC, both as a monotherapy[71] and in combination with an EGFR TKI for patients with concurrent activating EGFR mutations[72-74]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[75] and NSCLC[76] as a monotherapy as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[77-79] . Savolitinib elicited responses for patients with

MET-amplified gastric cancer either alone or in combination with docetaxel[80-81]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[82]. Patients with MET-amplified NSCLC[83] or MET-amplified gastric cancer[84] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapies such as the monoclonal HGF-targeting antibody rilotumumab as well as the combination of ramucirumab and the monoclonal MET-targeting antibody emibetuzumab[85]. The Phase 2 LUMINOSITY study of the MET antibody drug conjugate telisotuzumab vedotin (teliso-V) reported a 37% (19/52) ORR for patients with non-squamous EGFR-wildtype tumors; lower ORRs were observed for patients with squamous (11%, 3/27) or non-squamous EGFR-mutated (12%, 5/43) tumors[86]. A Phase 1 study showed that teliso-V plus osimertinib yielded an ORR of 56% (10/18) for patients with EGFR-mutated MET-overexpressing NSCLC who progressed on osimertinib, including ORRs of 56% (5/9) for patients with an EGFR L858R mutation and 67% (6/9) for those with an EGFR exon 19 deletion[87].

FREQUENCY & PROGNOSIS

In the Ovarian Serous Cystadenocarcinoma TCGA

dataset, amplification and mutation of MET has been found in 2% and 1% of cases, respectively[15]. In the literature, high-level polysomy or amplification of MET has been observed in 24% (21/89) of ovarian clear cell adenocarcinomas but in only 3% (3/86) of ovarian serous adenocarcinomas[88]. MET overexpression has been reported in 22% (20/90) of ovarian clear cell adenocarcinomas but not in any of the 89 ovarian serous adenocarcinomas studied[88]. Overexpression of c-Met was observed in 11% (15/138) patients with advanced ovarian or peritoneal cancer, which correlated with significantly poorer prognosis by univariate analysis and as a significant prognostic indicator of OS by multivariate analysis; patients with elevated c-Met expression correlated with reduced median OS[89].

FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[90-91]. MET has been reported to be amplified in cancer[92], with amplification positively correlating with protein expression in some cancer types[93-97] and associating with therapeutic response to MET inhibitors in a variety of cancer types[63-65,67-69,98-99].

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GENOMIC FINDINGS

GENE
TP53

ALTERATION
S127P

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
379T>C

VARIANT CHROMOSOMAL POSITION
chr17:7578551

VARIANT ALLELE FREQUENCY (% VAF)
59.2%

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[100-103] or p53 gene therapy such as SGT53[104-108]. 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[109]. 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[110]. 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[111]. 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[112]. 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[80]. 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[113]. 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[114]. 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[108]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[115]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[116].

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%[15,117-123]. TP53 alterations have also been reported in serous tubal intraepithelial carcinomas (STICs) of the Fallopian tube, which are suggested to be precursor lesions of tubo-ovarian high grade serous carcinomas[124-127]. Aberrant p53 expression has been associated with higher ovarian serous carcinoma grade (89-90% of high-grade vs. 6.6-9% of low-grade vs. 0% of benign)[128-130]. 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[122]. 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[131].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[132]. Alterations such as seen here may disrupt TP53 function or expression[133-137].

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[138-140], including sarcomas[141-142]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[143] to 1:20,000[142]. 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[144]. 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[145-150]. 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[145-146]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[151]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[149,152-153]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Erik Williams, M.D. | 10 October 2022
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GENOMIC FINDINGS

GENE
CSF3R

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Oncogenic CSF3R mutations may differentially activate downstream signaling, with membrane-proximal point mutations T618I and T640N (also known as T617N) activating the JAK/STAT pathway and C-terminal truncations primarily activating SRC family kinases[154]. Based on clinical[154-157] and preclinical[154,158-161] data for membrane-proximal mutations and preclinical data[161-163] for truncations, activating CSF3R mutations may predict sensitivity to JAK2 inhibitors such as ruxolitinib. Preclinical data regarding the use of dasatinib in the context of CSF3R truncation is mixed, with an initial study reporting sensitivity to dasatinib[154] and subsequent studies demonstrating a lack of activity in vitro[161-162]. A patient with atypical chronic myeloid leukemia harboring a CSF3R-SPTNA1 fusion with a breakpoint in the CSF3R C-terminal domain failed to respond to dasatinib[164]. Co-occurrence of membrane-proximal mutations and truncation results in an aggressive clinical course, and while preclinical data suggest that ruxolitinib or dasatinib are ineffective in this context[161], a patient with CNL harboring CSF3R T618I and Q739* experienced a temporary hematological response on ruxolitinib[165]. Limited preclinical data suggest that the MEK inhibitor trametinib may be effective in the context of compound CSF3R mutations[161]. A Phase 2 study of ruxolitinib in combination with regorafenib for patients with colorectal carcinoma and a Phase 3 trial of ruxolitinib with capecitabine for patients with metastatic pancreatic cancer were terminated early due to lack of efficacy; it is unclear if ruxolitinib may be beneficial in the context of solid tumors.

FREQUENCY & PROGNOSIS

Somatic alterations in CSF3R have been reported at low frequencies in multiple solid tumors, including tumors of the skin (6.1%), endometrium (2.8%), stomach (2.4%), large intestine (2.2%), and at lower incidences in other tumor types (COSMIC, Jan 2022)[166]. CSF3R activating mutations are frequently found in patients with atypical chronic myeloid leukemia (aCML) and chronic neutrophilic leukemia (CNL)(50-60%)[154,159,167]. CSF3R mutations have also been reported in 3% of chronic myelomonocytic leukemia (CMML) cases and were associated with decreased overall survival and AML-free survival[168].

FINDING SUMMARY

CSF3R encodes a receptor for granulocyte colony-stimulating factor (G-CSF), which drives myeloid progenitor cell survival and proliferation[169]. Activation of the CSF3 receptor can lead to increased CSF3 response and promote cell proliferation and differentiation through JAK signaling[159,170]. Truncating CSF3R mutations, occurring within the cytoplasmic domain (aa 651–836), or activating missense alterations, such as T618I, have been reported to be transforming and activate SRC family kinases and STAT3/5, with the JAK/STAT pathway reported to be activated to a lesser extent by cytoplasmic domain truncations than by missense variants[154,162-163].

GENE
MYCL1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available therapies to address alterations in MYCL1.

FREQUENCY & PROGNOSIS

MYCL1 amplification has been reported in a variety of cancer types, including Merkel cell carcinoma (9/23, 39%)[171], prostate cancer (35%)[172-173], ovarian carcinoma (16%)[174], medulloblastoma (3-15%)[175-176], small cell lung cancer (3-8%)[177-178], lung adenocarcinoma (7%)[179], esophageal squamous cell carcinoma (SCC, 3%)[180], cervical SCC (2%)[181], urothelial carcinoma (2%)[182], nasopharyngeal carcinoma (5/8, 62.5%)[183], as well as in a case of hepatocellular carcinoma (HCC)[184]. MYCL1 amplification was not prognostic in prostate cancer in one study[172]. MYCL1 overexpression has been noted in ovarian cancer[174]; Merkel cell carcinoma[171]; testicular germ cell tumors[185]; and gastric cancer, where MYCL1 overexpression is a negative prognostic marker[186]. MYCL1 is a microsatellite marker, and allelic loss is a negative prognostic factor in colorectal adenocarcinoma[187]. Loss of heterozygosity (LOH) of MYCL1 has been reported in 50% of recurrent and 37% of non-recurrent non-small cell lung cancer[188], as well as in 29% of HCCs in one study[189].

FINDING SUMMARY

MYCL1 encodes a protein that regulates transcription of genes involved in cell proliferation, differentiation, and apoptosis[190]. MYCL1 overexpression has been correlated with MYCL1 amplification in ovarian cancer[174] and Merkel cell carcinoma[171].

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GENE
PRKCI

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

In preclinical studies, the PKCi inhibitor aurothiomalate has been shown to have anti-tumorigenic effects in lung cancer and rhabdomyosarcoma cells[191-193]. A Phase 1 escalation trial of aurothiomalate in patients with advanced lung, ovarian, or pancreatic cancer reported 2/11 enrolled patients achieving stable disease[194]. Other PKCi inhibitors with improved PKCi selectivity, such as CRT0066854 and ICA-1, are in preclinical

development[195-196]. In preclinical models, PKCi activation has been reported to promote hedgehog signaling[197] as well as RAS signaling and to require the RAC1-MEK-ERK pathway for tumorigenesis[198-201]. Therefore, MEK inhibitors may be beneficial for a patient with PRKCI amplification. MEK inhibitors are in clinical trials in multiple cancer types. The MEK inhibitors cobimetinib and trametinib are approved for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations and are being studied in clinical trials in multiple cancer types[202-203].

FREQUENCY & PROGNOSIS
PRKCI has been reported to be frequently amplified in lung SCC, ovarian cancer, and esophageal SCC[197,204-205]. PRKCI amplification and/or protein overexpression has been associated with

inferior patient prognosis and/or adverse clinico-pathological features in esophageal SCC, cholangiocarcinoma, lung, breast, pancreatic, gastric, ovarian, and brain cancers[198-199,204-209]. In preclinical studies, genetic inhibition of PKCi expression has been shown to have anti-tumorigenic effects in xenografted and/or cultured cells of alveolar rhabdomyosarcoma, non-small cell lung cancer, glioma, and pancreatic, ovarian, and colon carcinoma[191-193,199-200,205-206].

FINDING SUMMARY
PRKCI encodes protein kinase C iota (PKCi), which has been reported to play roles in heart and spinal cord development[210-211]. In esophageal squamous cell carcinoma (SCC), PRKCI amplification strongly correlates with PKCi protein overexpression[204].

GENE
TERC

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

There are no therapies available to directly address genomic alterations in TERC.

FREQUENCY & PROGNOSIS
In the TCGA datasets, amplification of TERC has most frequently been observed in lung squamous cell carcinoma (SCC; 34-43%)[212], ovarian serous cystadenocarcinoma (21-34%)[15], esophageal carcinoma (26%), cervical SCC and endocervical adenocarcinoma (20%), head and neck SCC (19-20%)[213], non-small cell lung cancer (18%)[214], and uterine carcinosarcoma (14%; 8/57) (cBioPortal, Jan 2022)[92,215]. Studies have shown that TERC amplification is common in cervical cancer and that gain of the 3q chromosome arm predicts advanced grade and disease progression[216-217]. TERC amplification is also frequent in lung cancer;

studies have reported TERC upregulation in 51-96% of non-small cell lung cancer specimens[218-220] and association of increased gene copy number of TERC with squamous cell carcinoma histology[220].

FINDING SUMMARY
TERC, the human telomerase RNA gene (hTERC), encodes the RNA component of the telomerase enzyme. Telomerase is an RNA polymerase that maintains telomeric DNA and plays a role in senescence and oncogenesis[221].

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PATIENT	TUMOR TYPE	REPORT DATE
Kao, Chen Hsin	Ovary high grade serous carcinoma	10 Oct 2022

ORDERED TEST # ORD-1468925-01

THERAPIES WITH CLINICAL BENEFIT	IN PATIENT'S TUMOR TYPE

Niraparib

Assay findings association

Loss of Heterozygosity score
16.8%

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[1-2,222]. 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%[2,222].

SUPPORTING DATA

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)[3,223]. 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)[224]. 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)[225]. 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)[226]. 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[227].

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PATIENT
Kao, Chen Hsin

TUMOR TYPE
Ovary high grade serous
carcinoma

REPORT DATE
10 Oct 2022

ORDERED TEST # ORD-1468925-01

THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE

Olaparib

Assay findings association

**Loss of Heterozygosity
score**
16.8%

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[1-2,222] . 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%[2,222] .

SUPPORTING DATA

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[228-229] , and for patients with platinum-sensitive (vs. platinum-resistant) cancer[229-232] . 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[233] and multiple later-phase studies[234-238] . At the 5-year follow-up of SOLO-1, olaparib continued to improve mPFS compared with placebo for patients with ovarian cancer[239]. 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[240]. Olaparib has also been evaluated in combination with other therapies. A statistically superior median PFS (mPFS) 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 (22.1 vs. 16.6 months), the BRCA1/2-mutated population (37.2 vs. 21.7 months), and the BRCA1/2-wildtype population harboring homologous recombination deficiency (HRD)-positive status (28.1 vs. 16.6 months)[241]. For patients with platinum-sensitive recurrent ovarian cancer who previously progressed on chemotherapy, statistically increased mPFS was reported in a Phase 2 study of olaparib in combination with chemotherapy (12.2 months) compared with chemotherapy alone (9.6 months)[242], as well as from treatment with the VEGFR inhibitor cediranib compared with olaparib monotherapy in a Phase 1/2 trial[243]. Combination treatment with cediranib and olaparib also demonstrated numerically longer mPFS compared with chemotherapy alone for patients with BRCA1/2-mutated platinum-sensitive recurrent ovarian cancer (10.5 vs. 18 months); however, improved clinical benefit was not observed for patients without BRCA1/2 mutation (mPFS 9.7 vs. 8.9 months) or for the overall intent-to-treat population (mPFS 10.3 vs. 10.4 months, ORR 71.3% vs. 69.4%)[244]. 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[245]. 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 with 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[246].

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| THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE |

Rucaparib

Assay findings association

Loss of Heterozygosity score
16.8%

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[1-2,222]. 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%[2,222].

SUPPORTING DATA

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)[247]. 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].

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PATIENT
Kao, Chen Hsin

TUMOR TYPE
Ovary high grade serous
carcinoma

REPORT DATE
10 Oct 2022

ORDERED TEST # ORD-1468925-01

| THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE |

Cabozantinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE
Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved as monotherapy to treat patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer (MTC), and differentiated thyroid cancer (DTC). It is also approved in combination with nivolumab to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION
Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent

MET amplification[248-249] , as well as by extensive preclinical data[250-256] .

SUPPORTING DATA
A Phase 2 study comparing cabozantinib to paclitaxel for patients with recurrent or persistent ovarian cancer reported similar median PFS (5.3 vs. 5.5 months, HR=1.1) but lower ORR (7.0% [4/57] vs. 24.1% [13/54, 2 CRs]) and shorter median OS (19.4 months vs. not reached, HR=2.27) with cabozantinib[257]. In a Phase 2 trial of cabozantinib for solid tumors, patients with ovarian cancer experienced a 21.4% (15/70, 1 CR) ORR and 50.0% (35/70) DCR, with median PFS of 5.5 months[258].

Capmatinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE
Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION
On the basis of clinical data in non-small cell lung cancer[76-79,259-260] , hepatocellular carcinoma[75], renal cell carcinoma[261], and gastric cancer[80], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA
Clinical data on the efficacy of capmatinib for the

treatment of ovarian cancer are limited (PubMed, Oct 2022). Capmatinib has been investigated primarily for the treatment of NSCLC, demonstrating efficacy as monotherapy for patients with MET amplification[262-264] or MET exon 14 skipping alterations[71,263] as well as in combination with EGFR inhibitors for patients with MET amplification[72-74] . Multiple Phase 1 and 2 clinical studies have reported limited efficacy for capmatinib monotherapy in non-NSCLC indications, with no responses observed for patients with MET-amplified glioblastoma (n=10)[265], MET-overexpressing gastric cancer (n=9)[266], or other advanced solid tumors with MET amplification or overexpression (n=11)[266-267] .

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Crizotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), adult and pediatric patients with ALK-positive inflammatory myofibroblastic tumor (IMT), and pediatric and young adult patients with ALK-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[63-65,268-269], gastric cancer[98], gastroesophageal cancer[67], glioblastoma[68], and carcinoma of unknown primary[69], as well as in patients with MET-mutated cancers, including NSCLC[248,270-274], renal cell carcinoma (RCC)[275], and histiocytic sarcoma[270]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[248,270,272-274,276].

SUPPORTING DATA

Clinical data on the efficacy of crizotinib for the treatment of primary ovarian, Fallopian tube, or peritoneal carcinomas are limited (PubMed, Sep 2022). A case report of one patient with chemotherapy resistant high-grade serious ovarian carcinoma harboring GOPC-ROS1 fusion experienced partial response following treatment with crizotinib[277]. Clinical benefit has been reported from crizotinib treatment in case studies of patients with ALK-positive ovarian or pelvic adnexal lesions thought to represent metastases from primary NSCLC[278-281], although one patient with primary ALK-positive NSCLC developed a progressing ALK-positive pelvic adnexal mass in the course of crizotinib treatment[282]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[283-287], ROS1 rearrangements[288-292], an NTRK1 fusion[293], or MET activation[63-65,248,268-269,271-274,294-300]. Crizotinib has also benefited patients with MET-mutated renal cell carcinoma[301] and patients with MET-amplified gastroesophageal cancer, glioblastoma, and carcinoma of unknown primary[67-69]. While a Phase 1b study evaluating crizotinib for the treatment of patients with ALK-positive malignancies, reported ORR of 52.9% (9/17) and 66.7% (6/9) in patients with lymphoma and inflammatory myofibroblastic tumors (IMT), respectively, an ORR of 11.8% (2/17) was reported for patients with other types of tumors[302]. Whereas median PFS and median OS were not reached for patients with lymphoma or IMT, median PFS was 1.3 months and median OS was 8.3 months for patients with other tumor types, and the median duration of treatment was ~1 month relative to 1-3 years for patients with lymphoma or IMT[302]. A Phase 1 clinical trial of crizotinib in pediatric solid tumors reported objective responses in 14/79 patients, including nine CRs and five PRs; response was enriched in patients with activating alterations in ALK[303].

Talazoparib

Assay findings association

Loss of Heterozygosity score
16.8%

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[1-2,222]. 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%[2,222].

SUPPORTING DATA

An ORR of 42% (5/12) was reported for patients with BRCA1/2-mutated ovarian cancer treated with talazoparib in a Phase 1 study[304]. 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[305].

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PATIENT
Kao, Chen Hsin

TUMOR TYPE
Ovary high grade serous
carcinoma

REPORT DATE
10 Oct 2022

ORDERED TEST # ORD-1468925-01

THERAPIES WITH CLINICAL BENEFIT	IN OTHER TUMOR TYPE

Tepotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[76-79,259-260], hepatocellular carcinoma[75], renal cell carcinoma[261], and gastric cancer[80], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of tepotinib for the treatment of ovarian cancer are limited (PubMed, Jul 2022). Tepotinib has primarily been investigated in non-small cell lung cancer and has demonstrated efficacy as a single agent for patients with MET amplification[76] and MET exon 14-skipping alterations[306-307]. Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[78-79]. In advanced hepatocellular carcinoma, Phase 2 studies of tepotinib reported improved ORR and PFS for both treatment-naive and previously treated patients with MET protein overexpression[75,308-310]. In a Phase 1 study of advanced solid tumors, tepotinib monotherapy yielded an ORR of 1.3% and a DCR of 24%, with 2 confirmed PRs observed for patients with esophageal or lung cancer and 2 unconfirmed PRs for patients with colorectal or nasopharyngeal cancer[311]. In another Phase 1 study of solid tumors, tepotinib yielded a DCR of 17% (2/12), with 2 SD of ≥12 weeks observed in a patient with gastric cancer and another with urachal cancer[312].

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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PATIENT
Kao, Chen Hsin

TUMOR TYPE
Ovary high grade serous
carcinoma

REPORT DATE
10 Oct 2022

CLINICAL TRIALS

ORDERED TEST #   ORD-1468925-01

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
16.8%

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)

NCT04884360
PHASE 3

D9319C00001- 1L OC Mono Global RCT

TARGETS
PARP

LOCATIONS: Rui'an (China), Wenzhou (China), Jiaxing (China), Shanghai (China), Suzhou (China), Wuxi (China), Nanjing (China), Hefei (China), Guangzhou (China), Urumqi (China)

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: Jinhua (China), Hangzhou (China), Shanghai (China), Nantong (China), Nanjing (China), Hefei (China), Guangzhou (China), Zhuhai (China), Zhengzhou (China), Changsha (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)

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PATIENT
Kao, Chen Hsin

TUMOR TYPE
Ovary high grade serous
carcinoma

REPORT DATE
10 Oct 2022

ORDERED TEST # ORD-1468925-01

CLINICAL TRIALS

NCT04517357
PHASE 2

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

TARGETS
RET, SRC, VEGFR2, KIT, PARP

LOCATIONS: Hangzhou (China)

NCT03742895
PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Nedlands (Australia), Darlinghurst (Australia), Adana (Turkey), Ankara (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Tel Aviv (Israel)

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)

FOUNDATIONONE®CDx

PATIENT
Kao, Chen Hsin

TUMOR TYPE
Ovary high grade serous
carcinoma

REPORT DATE
10 Oct 2022

CLINICAL TRIALS

ORDERED TEST # ORD-1468925-01

GENE
MET

ALTERATION
amplification

RATIONALE
Activating MET alterations may confer sensitivity to MET inhibitors.

NCT03175224
	PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), North Adelaide (Australia), Bedford Park (Australia)

NCT04647838
	PHASE 2

Tepotinib in Solid Tumors Harboring MET Alterations

TARGETS
MET

LOCATIONS: Cheonan (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

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)

NCT04116541
	PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

LOCATIONS: Nice (France), Lyon (France), Marseille (France), Toulouse (France), Bordeaux (France)

NCT04693468
	PHASE 1

Talazoparib and Palbociclib, Axitinib, or Crizotinib for the Treatment of Advanced or Metastatic Solid Tumors, TalaCom Trial

TARGETS
PARP, CDK4, CDK6, VEGFRs, ALK, ROS1, AXL, TRKA, MET, TRKC

LOCATIONS: Texas

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PATIENT
Kao, Chen Hsin

TUMOR TYPE
Ovary high grade serous carcinoma

REPORT DATE
10 Oct 2022

ORDERED TEST #   ORD-1468925-01

CLINICAL TRIALS

NCT05038839

PHASE 1

Cabozantinib and Pamiparib for the Treatment of Advanced of Refractory Solid Tumors

TARGETS
MET, ROS1, RET, VEGFRs, PARP

LOCATIONS: Texas

FOUNDATIONONE®CDx

PATIENT
Kao, Chen Hsin

TUMOR TYPE
Ovary high grade serous carcinoma

REPORT DATE
10 Oct 2022

CLINICAL TRIALS

ORDERED TEST # ORD-1468925-01

GENE
TP53

ALTERATION
S127P

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)

Electronically signed by Erik Williams, M.D. | 10 October 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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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

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APPENDIX   Variants of Unknown Significance

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.

AR
D551E

BCOR
P483L

ERBB2
P1102S and amplification[†]

HDAC1
rearrangement

NOTCH3
R1175W

PRDM1
amplification

SMARCA4
E1636G

[†] An ERBB2 amplification of copy number 4 was detected. While this result is considered a variant of unknown significance across tumor types, in a clinical concordance study of breast cancer samples with an FDA-approved FISH test, 70% (7 out of 10 samples) with copy number 4 were positive with an average ratio of 2.3, and 30% (3 out of 10) samples were negative by the FISH test.

FOUNDATIONONE®CDx

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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	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

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APPENDIX   About FoundationOne®CDx

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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 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. 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

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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

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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) 7.2.0

The median exon coverage for this sample is 879x

Electronically signed by Erik Williams, M.D. | 10 October 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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PATIENT
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TUMOR TYPE
Ovary high grade serous carcinoma

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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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PATIENT
Kao, Chen Hsin

TUMOR TYPE
Ovary high grade serous
carcinoma

REPORT DATE
10 Oct 2022

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APPENDIX   References

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