PATIENT
DISEASE Prostate acinar adenocarcinoma
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
BRCA2 loss	Lynparza® (Olaparib)

For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be performed.

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite Status MS-Stable §
Tumor Mutational Burden 1 Muts/Mb §
RAD21 amplification §
TP53 R283C

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

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) and tumor mutational burden (TMB) 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 the targeted therapies listed in Table 1 in accordance with the 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. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

The test is also used for detection of genomic loss of heterozygosity (LOH) from FFPE ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the RUBRACA product label.

The F1CDx assay will be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	Tabrecta™ (Capmatinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E and V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre™ (Pemigatinib)
Prostate Cancer	*HRR* alterations	Lynparza® (Olaparib)

ABOUT THE TEST FoundationOne®CDx is the first FDA-approved broad companion diagnostic for solid tumors.

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Note: The intended use (IU) statement and claims made on this sample report may not be up to date. For the latest version of the FoundationOne CDx claims and IU, please see the current label: www.foundationmedicine.com/f1cdx

ABOUT THE TEST FoundationOne®CDx is the first and only FDA-Approved comprehensive companion diagnostic for all solid tumors.

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

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Biomarker Findings

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.

BRCA2 loss
RAD21 amplification - equivocal†
TP53 R283C

† See About the Test in appendix for details.

4 Therapies with Clinical Benefit
0 Therapies with Lack of Response
10 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
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

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
***BRCA2* -** loss	Olaparib	1	Niraparib
10 Trials *see p. 8*	Rucaparib	2A	Talazoparib

☐ *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.

***RAD21* - amplification - equivocal** ..... p. 4
***TP53* - R283C** ..... p. 5

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

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.

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI has been reported in 3.1-14.6% of prostate cancer samples[6-10]. A study of prostate cancer in hereditary nonpolyposis colorectal cancer (HNPCC) families reported MSI-H in 4-50% of cases[11-13]. For patients with advanced prostate cancer, dMMR/MSI status was associated with shorter median OS compared with patients with proficient MMR (3.8 vs. 7.0 years) by univariate and multivariate analysis (adjusted HR=4.09; P=0.005)[14].

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[15]. 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[15-17]. 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[18-20]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15,17,19-20].

BIOMARKER

Tumor Mutational Burden

RESULT
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[21-23] and anti-PD-1 therapies[21-24]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[21-24]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[21]. 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[25] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[22]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in patients with TMB ≥10 Muts/Mb compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[24]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Prostate acinar adenocarcinoma harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 3.4% of cases have high TMB (>20 muts/Mb)[26]. Prostate cancer has been reported to harbor a relatively low TMB among solid tumors[27-28], with approximately 0.5-1.5 (muts/Mb) in localized tumor samples[29-31], and a higher but still low TMB of 2-5 muts/Mb in metastatic, castration-resistant prostate cancer (mCRPC) samples[32-34]. One study reported that 4 of 150 (2.7%) mCRPC cases harbored high TMB (nearly 50 muts/Mb), which was due to defects in mismatch repair genes MLH1 and MSH2 in 3 of the 4 cases[34]. The effects of hypermutation on prognosis and clinical features in prostate cancer have not been extensively investigated (PubMed, Feb 2020).

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[35-36] and cigarette smoke in lung cancer[37-38], treatment with temozolomide-based chemotherapy in glioma[39-40], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[41-45], and microsatellite instability (MSI)[41,44-45]. 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[22-23].

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GENE
BRCA2

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[46-63] or to ATR inhibitors[64-65]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[47,52,55,62-63] and for patients with platinum-resistant or -refractory disease[46,51,58,61]. In a case study, a patient with therapy-induced neuroendocrine prostate cancer and an inactivating BRCA2 rearrangement experienced a CR ongoing for 20 months to the ATR inhibitor berzosertib[65]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[66], ovarian carcinoma[67], and triple-negative breast cancer (TNBC)[68] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA2-deficient cells to ATR inhibitors. The Phase 3 PROfound study for patients with metastatic castration-resistant prostate cancer (CRPC) who had progressed on a new hormonal agent reported improved radiographic PFS with olaparib compared with physician's choice of abiraterone/prednisone or enzalutamide for patients with BRCA1/2 or ATM alterations (7.4 vs. 3.6 mo., HR=0.34)[69].

Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as the platinum chemotherapies cisplatin and carboplatin[70-72].

FREQUENCY & PROGNOSIS

BRCA2 genomic loss has been described in 1–2% of primary and 2–3% of metastatic prostate cancer cases[31,34,73]. BRCA2 mutations have been identified in 3–6% of primary and 6–7% of metastatic prostate cancer specimens[31,34,73], with deleterious germline BRCA2 mutations present in 5% of men with metastatic prostate cancer[74]. The positive predictive value of prostate specific antigen (PSA) levels was found to be higher in patients with BRCA1/2 mutations than in the general population[75]. BRCA2 germline mutations have been associated with attributes of aggressive prostate cancer at diagnosis, including high Gleason score, nodal involvement, advanced tumor stage, and metastatic spread[76]. Germline BRCA2 mutation carriers had a significantly shorter cause-specific survival (CSS, 8.6 vs. 15.7 years) than noncarriers[76]. Following radical conventional treatment for localized prostate cancer, patients with germline BRCA1/2 mutations experienced significantly shorter metastasis-free survival (HR=2.36) and CSS (HR=2.17) than noncarriers[77]. For patients with metastatic castration-resistant prostate cancer (mCRPC), germline BRCA2 mutations were an independent marker of poor prognosis (CSS 17.4 vs. 33.2 months, HR=2.11) in 1 study[78]. Germline BRCA2 mutations in mCRPC were associated with relative benefit from first-line abiraterone or enzalutamide compared with taxanes (CSS 24.0 vs. 17.0 months, PFS on the second systemic therapy 18.9 vs. 8.6 months) in a large prospective cohort study[78]. Three patients with non-neuroendocrine prostate cancer harboring BRCA2 mutations derived clinical benefit from treatment with platinum-based chemotherapy[79-80].

FINDING SUMMARY

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[81]. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis[82]. BRCA2 alterations that disrupt PALB2 binding (aa 21-39)[83], the BRC repeats (aa 1002-2085), the DNA binding domain (aa 2479-3192), and/or the C-terminal RAD51 binding domain, as observed here, are predicted to be inactivating[81,84-99]. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[100-101], and the lifetime risk of breast and ovarian cancer in BRCA2 mutation carriers has been estimated to be as high as >80% and 23%, respectively[102]. Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%[103]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[102,104-109]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

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