FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Prostate acinar adenocarcinoma
COUNTRY CODE
BR

REPORT DATE

ORDERED TEST #

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 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

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 5 Muts/Mb

Genomic Findings

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

AR T878A
CDKN1B loss

14 Disease relevant genes with no reportable alterations: ***ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L***

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Bicalutamide** (p. 7), **Nilutamide** (p. 7)
- Targeted therapies with **potential resistance** based on this patient's genomic findings: ⊗ **Abiraterone** (p. 8), **Flutamide** (p. 8)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 5 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS

AR **-** T878A

8 Trials *see p. 9*

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Bicalutamide	1	none
Nilutamide	1	
Abiraterone	⊗	
Flutamide	⊗	

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *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.

CDKN1B - loss ..... p. 6

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

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remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

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

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BIOMARKER

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[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].

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BIOMARKER

Tumor Mutational Burden

RESULT
5 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[21-23], anti-PD-1 therapies[21-24], and combination nivolumab and ipilimumab[25-30]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[21-24,31-35]. 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[31]; similar findings were observed in the KEYNOTE 028 and 012 trials[24]. 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)[35]. 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[36]. 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[34]. 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[37] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[22]. The Phase 2 CheckMate 650 trial of nivolumab and ipilimumab treatment for patients with metastatic castration-resistant prostate cancer reported that patients harboring above the median study TMB experienced increased ORR and PSA responses[30]. A real-world study for patients with pretreated metastatic castration-resistant prostate cancer (mCRPC) reported longer time to next therapy (TTNT) for patients with high tumor mutational burden (TMB; ≥10 Muts/Mb) treated with immune checkpoint inhibitors (ICIs) compared with those treated with taxane chemotherapies, whereas for patients with low TMB (<10 Muts/Mb), treatment with ICIs resulted in worse TTNT compared with taxanes[38].

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)[39]. Prostate cancer has been reported to harbor a relatively low TMB among solid tumors[40-41], with approximately 0.5-1.5 (muts/Mb) in localized tumor samples[42-44], and a higher but still low TMB of 2-5 muts/Mb in metastatic, castration-resistant prostate cancer (mCRPC) samples[45-47]. 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[47]. The effects of hypermutation on prognosis and clinical features in prostate cancer have not been extensively investigated (PubMed, Feb 2022).

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[48-49] and cigarette smoke in lung cancer[50-51], treatment with temozolomide-based chemotherapy in glioma[52-53], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[54-58], and microsatellite instability (MSI)[54,57-58]. 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[22-23,31].

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GENE
AR

ALTERATION
T878A

TRANSCRIPT ID
NM_000044

CODING SEQUENCE EFFECT
2632A>G

VARIANT ALLELE FREQUENCY (% VAF)
77.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Antiandrogens such as apalutamide, bicalutamide, cyproterone, darolutamide, enobosarm, enzalutamide, flutamide, and nilutamide directly target AR, whereas hormone therapies such as the CYP17A1 inhibitor abiraterone and luteinizing hormone-releasing hormone agonists or antagonists modulate androgen production[59-67]. Resistance to androgen deprivation therapy (ADT) commonly occurs in prostate cancer through mechanisms such as increased AR expression, AR activation by tyrosine kinase–dependent signaling, alterations in AR co-activators, expression of alternatively spliced isoforms of AR mRNAs (AR-Vs), and extragonadal synthesis of androgenic compounds[68-72]. AR signaling may promote radioresistance in prostate cancer by transcriptionally upregulating DNA repair genes[73]. There is preclinical evidence that development of resistance to anti-AR therapies, such as abiraterone and enzalutamide, may engender cross-resistance to the taxanes docetaxel and cabazitaxel[74]; however, certain AR-Vs may remain sensitive to taxanes[75-76]. Approaches currently in clinical and preclinical development for prostate cancer include therapies that target AR nuclear translocation and degradation pathways[77-83], single-agent or combinational approaches to suppress androgen biosynthesis[84], and the use of bromodomain and extraterminal (BET) inhibitors that disrupt the interaction between AR and $BRD4$[85-88]; the latter approach has potential to target AR-Vs[86-87,89]. Galeterone, a multifunctional AR inhibitor, has been evaluated in several Phase 1 and Phase 2 studies and has been found to reduce prostate-specific antigen levels for 49-73% of patients, although clinical trials of this reagent are not recruiting patients with prostate cancer[90].

— Potential Resistance —

Clinical evidence indicates that patients with T878 mutations experience progression on flutamide[91-93], and resistance is further supported by preclinical studies[92,94-111]; therefore, patients with AR T878 mutations are unlikely to benefit from flutamide treatment. Clinical progression in the context of AR T878A has also been reported upon treatment with abiraterone[112-117], suggesting that patients with this AR mutation are also unlikely to benefit from the inhibitor. The clinical benefit of enzalutamide for patients with T878A is unclear due to conflicting clinical[113,115-116,118] and preclinical[95,97,107,111,119-123] data; thus, it is unclear whether patients with mutations at this site would benefit from enzalutamide. Cyproterone[96,98,100,102,105,108-110] and nilutamide[95,124-125] lead to activation of AR T878 mutants, and it is unclear whether these therapies would be appropriate here. In contrast, limited clinical[92] and extensive preclinical[95-109,119-120,125-126] evidence indicates that AR T878 mutations remain sensitive to bicalutamide.

FREQUENCY & PROGNOSIS

AR mutations have been reported in ~5% of prostate carcinomas[127-129]. Evidence for the prognostic value of AR mutations in prostate cancer has been conflicting; a study demonstrated that AR mutations were associated with worse PFS and OS following enzalutamide or abiraterone treatment[130], whereas another study did not find a statistically significant correlation between AR mutations and time to progression in the same setting[131]. Moreover, a study found no significant correlation between AR mutations in the ligand binding domain (LBD) and a worse rate of ≥ 50% prostate specific antigen (PSA) decline from baseline ($p=0.072$); however, AR LBD mutations were associated with a worse 30% or more decline in PSA ($p=0.039$)[117].

FINDING SUMMARY

AR encodes the androgen receptor, a nuclear receptor that binds to testosterone and dihydroxytestosterone. AR mutations at T878, also known as T877, are resistance mutations that exhibit neomorphic activity by inducing an antagonist-to-agonist switch for cyproterone[96,98,100,102,105,108-110], flutamide[92,94-111], and nilutamide[95,124-125]. T878 mutations retain sensitivity to bicalutamide, which lacks agonist activity for T878 mutations[95-100,102-109,125-126].

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GENE
CDKN1B

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in CDKN1B.

FREQUENCY & PROGNOSIS

CDKN1B mutations have been reported in tumors of the small intestine (8.5%), gastrointestinal tract (4.5%), endometrium (2.2%), parathyroid (1.9%), urinary tract (1.5%), prostate (1.4%), and stomach (1.3%) (COSMIC, Jan 2022)[132]. A survey of 350 breast cancers found somatic mutations in CDKN1B in approximately 1% of cases[133]. Mutations in p27 have been associated with multiple endocrine neoplasia syndrome, and truncating alterations have been shown to disrupt normal subcellular localization of p27 due to the loss of a nuclear localization motif[134-135]. Loss of p27 expression has been described in some studies as a negative indicator of prognosis for patients with B-cell lymphomas, but the relationship between p27 levels and cell proliferation is somewhat controversial[136]. Loss of p27 expression has also been reported as a poor prognostic factor in gastroenteropancreatic neuroendocrine tumors[137]. Changes in the levels of p27 have been observed in the context of multiple myeloma, and decreased levels of p27 are associated with reduced overall survival and more aggressive cancers[138-140]. A preclinical study showed that p27 is essential for cell cycle arrest of T-cell acute lymphoblastic leukemia (T-ALL) cells by glucocorticoid treatment[141].

FINDING SUMMARY

CDKN1B encodes the cyclin-dependent kinase inhibitor p27, which controls cell cycle progression through G1 phase by binding to prevent action of cyclin E/CDK2 and cyclin D/CDK4 protein complexes. Removal of this inhibition is required for cellular transition from quiescence to a proliferative state. There is some evidence that germline variants in CDKN1B are associated with increased risk for several tumor types, including prostate[142], endometrial[143], and colorectal cancers[144].

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Bicalutamide

Assay findings association

AR
T878A

AREAS OF THERAPEUTIC USE

Bicalutamide is an orally available AR inhibitor that is FDA approved for use, in combination with LHRH agonists, in stage D2 metastatic prostate carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical[92,145] and preclinical studies have demonstrated that AR activation may predict sensitivity to bicalutamide[95-96,108,120] ; AR amplification may predict sensitivity to bicalutamide combined with other androgen-deprivation agents[146-147] . Clinical[92] and preclinical[95-97,100,110,120] studies suggest that AR T878 mutations retain sensitivity to bicalutamide.

SUPPORTING DATA

A long-term follow-up to a Phase 3 clinical trial of bicalutamide/luteinizing hormone-releasing hormone (LHRH) analog combination therapy in prostate carcinoma reported significant improvement in OS (HR=0.78, p=0.0498) compared with LHRH analog monotherapy[146]. In a randomized Phase 2 study for patients with metastatic or non-metastatic castration-resistant prostate cancer (CRPC), enzalutamide reduced the risk of progression or death (median PFS not reached vs. 8.6 months, HR=0.24, p<0.0001) compared with bicalutamide[148].

Nilutamide

Assay findings association

AR
T878A

AREAS OF THERAPEUTIC USE

Nilutamide is an orally available anti-androgen that is FDA approved for use, in combination with surgical castration, in stage D2 metastatic prostate carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Patients with prostate cancer may benefit from androgen receptor inhibitors such as nilutamide[149]. As preclinical evidence indicates that T878 mutations are resistant to nilutamide[95,124-125] , it is unclear whether the therapy would be beneficial in this case.

SUPPORTING DATA

A study in patients with androgen-independent prostate cancer reported a decrease in prostate-specific antigen (PSA) levels in 40% of patients receiving nilutamide[150]. Another Phase 2 study in patients with advanced prostate cancer who failed androgen ablation therapy reported initial and sustained (greater than 3 months) PSA responses in 64% and 29% of patients treated with nilutamide, respectively[151]. A Phase 2 study of nilutamide in patients with prostate cancer (n=16) after previous treatment with bicalutamide or flutamide demonstrated a partial response in 3 patients, but the study was discontinued due to having only have 3 PRs[152].

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Abiraterone

Resistance of variant(s) to associated therapy is likely

Assay findings association

AR
T878A

AREAS OF THERAPEUTIC USE

Abiraterone is an orally available CYP17 inhibitor that is FDA approved, in combination with prednisone, to treat metastatic castration-resistant prostate cancer (CRPC) and metastatic high-risk castration-sensitive prostate cancer (CSPC). Abiraterone blocks the synthesis of androgen by inhibiting CYP17, an enzyme involved in androgen biosynthesis. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical[115,153-155] and preclinical[65,119] studies have demonstrated that AR activation may predict sensitivity to abiraterone[115]. On the basis of extensive clinical evidence[112-117] , patients with AR T878A are unlikely to respond to abiraterone treatment, and the therapy is not predicted to be beneficial in this case.

SUPPORTING DATA

Phase 3 studies have shown that abiraterone plus prednisone compared with placebo plus prednisone significantly improved median OS in patients with metastatic castration-resistant prostate cancer (mCRPC) who were either chemotherapy-naive[156] or had previously received chemotherapy[157]. For patients with non-metastatic CRPC, abiraterone plus prednisone also showed clinical efficacy in the Phase 2 IMAAGEN study, with a median time to prostate-specific antigen (PSA) progression of 28.7 months and a median time to radiographic progressive disease of 41.4 months[158]. Abiraterone has also been evaluated to treat mCRPC in combination with other agents. A meta-analysis of 2 Phase 3 STAMPEDE studies for patients with high-risk non-metastatic CRPC, one comparing androgen deprivation therapy (ADT) to ADT plus abiraterone and prednisolone and another comparing ADT to ADT plus abiraterone, prednisolone, and enzalutamide demonstrated that metastasis-free survival was significantly longer in the combination-therapy groups than in the control groups (HR=0.53), with no difference in metastasis-free survival between the combination-therapy groups (HR=1.02)[159]. The Phase 3 LATITUDE study in patients with previously untreated high-risk metastatic castration-naive prostate cancer demonstrated that abiraterone plus prednisone and ADT significantly improved median OS (53.3 vs. 36.5 months, HR=0.66) and radiographic PFS (33.0 vs. 14.8 months, HR=0.47) compared with ADT plus placebo[160-161] . For patients with mCRPC, clinical benefit has been reported from abiraterone in combination with docetaxel[162] in the chemotherapy-naive setting and in combination with cabazitaxel[163] in the post-docetaxel, post-abiraterone setting. Cabazitaxel was more effective than abiraterone for patients with mCRPC who previously progressed on docetaxel and enzalutamide (8.2 vs. 3.4 months, HR=0.44)[164].

Flutamide

Resistance of variant(s) to associated therapy is likely

Assay findings association

AR
T878A

AREAS OF THERAPEUTIC USE

Flutamide is an orally available anti-androgen that is FDA approved for use, in combination with LHRH agonists, in stage B2-C and stage D2 metastatic prostate carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Patients with prostate cancer may benefit from androgen receptor inhibitors such as flutamide[165]. On the basis of extensive clinical evidence[91-93] and preclinical[92,94-111] evidence, patients with AR T878 mutations are unlikely to respond to flutamide treatment, and the therapy is not predicted to be beneficial in this case.

SUPPORTING DATA

A Phase 2 clinical trial of the combination of suramin, leuprolide, and flutamide in previously untreated patients with metastatic prostate cancer reported an overall response rate of 67%, include three complete responses and 30 partial responses[166]. A 10-year follow-up to a Phase 3 clinical trial in prostate carcinoma reported that long-term (24 months) androgen-deprivation therapy (flutamide/goserelin) with radiation conferred significant benefit compared with short-term (4 months) androgen-deprivation therapy with radiation[167].

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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CLINICAL TRIALS

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

GENE
AR

ALTERATION
T878A

RATIONALE
Tumors with AR activation may be responsive to therapies that inhibit the androgen receptor. On the basis of clinical studies, AR T878A may confer resistance to abiraterone and flutamide. Clinical and preclinical studies report conflicting efficacy of enzalutamide for AR T878A. Preclinical studies indicate that AR T878 mutations confer lack of response to cyproterone and nilutamide.

NCT02064036

PHASE NULL

Stereotactic Boost and Long-Term Androgen Deprivation for Adenocarcinoma of the Prostate

TARGETS
AR, LHRH

LOCATIONS: California

NCT04049747

PHASE NULL

Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer

TARGETS
AR

LOCATIONS: Southampton (United Kingdom), Chertsey (United Kingdom), Kingston upon Thames (United Kingdom), Isleworth (United Kingdom), London (United Kingdom), High Heaton (United Kingdom), Sunderland (United Kingdom)

NCT03070886

PHASE 2/3

Antiandrogen Therapy and Radiation Therapy With or Without Docetaxel in Treating Patients With Prostate Cancer That Has Been Removed by Surgery

TARGETS
LHRH, AR

LOCATIONS: San Juan (Puerto Rico), Florida, South Carolina

NCT04025372

PHASE 2

INTREPId (INTermediate Risk Erection PreservatIon Trial)

TARGETS
AR

LOCATIONS: New York, Connecticut, Massachusetts, Missouri

NCT03809000

PHASE 2

A Study of Salvage Radiotherapy With or Without Enzalutamide in Recurrent Prostate Cancer Following Surgery

TARGETS
AR

LOCATIONS: Florida, Georgia, Virginia, North Carolina, South Carolina

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NCT03541928

PHASE 2

Phase II High Risk Prostate Cancer Trial Using Gene & Androgen Deprivation Therapies, Radiotherapy, & Surgery

TARGETS
LHRH, AR

LOCATIONS: Texas

NCT04943536

PHASE 1

Bicalutamide Implants (Biolen) With Radiation Therapy in Patients With Localized Prostate Cancer

TARGETS
AR

LOCATIONS: Maryland

NCT04284761

PHASE 1

A Study to Establish the Feasibility of Biolen for the Local Delivery of Bicalutamide in Patients With Prostate Cancer

TARGETS
AR

LOCATIONS: Tauranga (New Zealand), Melbourne (Australia), Wollongong (Australia), Wahroonga (Australia)

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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.

GNAS
P147Q and P150T

HGF
V631M

MAP2K4
M396T and V321E

P2RY8
A347T

TNFAIP3
S423A

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APPENDIX Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

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

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT

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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 6.3.0

The median exon coverage for this sample is 947x

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