FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
Tomar , R.K.	**10 June 2016**	**Prostate acinar adenocarcinoma**

Date of Birth	05 September 1959	**Medical Facility**	Max Healthcare	**Specimen Received**	03 June 2016
Sex	Male	**Ordering Physician**	Verma, Amit	**Specimen Site**	Not Provided
FMI Case #	TRF158423	**Additional Recipient**	Not Given	**Date of Collection**	31 May 2016
Medical Record #	Not Given	**Medical Facility ID #**	201107	**Specimen Type**	Block
Specimen ID	H-1697/16	**Pathologist**	Not Provided		

ABOUT THE TEST:

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

3 genomic alterations

16 therapies associated with potential clinical benefit

0 therapies associated with lack of response

9 clinical trials

TUMOR TYPE: PROSTATE ACINAR ADENOCARCINOMA

Genomic Alterations Identified†

AR amplification
RET amplification
TP53 I162N

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
AR amplification	Abiraterone Bicalutamide Degarelix Enzalutamide Flutamide Goserelin Leuprolide Nilutamide Triptorelin	None	Yes, see clinical trials section
RET amplification	None	Cabozantinib Lenvatinib Ponatinib Regorafenib Sorafenib Sunitinib Vandetanib	Yes, see clinical trials section
TP53 I162N	None	None	None

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Note: Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have little or no 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.

GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
● ***AR*** amplification	**Gene and Alteration:** AR encodes the androgen receptor, a nuclear receptor that binds to testosterone and dihydroxytestosterone. AR is often amplified and overexpressed in castration-resistant prostate cancer (CRPC), also called hormone-refractory prostate cancer[1]. **Frequency and Prognosis:** Amplification of AR was reported in 44% of metastatic CRPC cases[2,3]. AR amplification in prostate cancer is reported to occur in response to androgen-deprivation therapy, as studies reported that 28-30% of patients with CRPC had AR amplification after, but not before, receiving androgen-deprivation therapy[4,5]. Studies have found AR gene amplification in 13-33% of patients with CRPC[4,5,6,7]. AR gene amplification is associated with advanced, hormone-refractory disease, and thus with poor prognosis. A study of prostate tumors that recurred during hormone therapy found no difference in patients with or without AR amplification in histological grade, Gleason score, or tumor stage[8]. Phosphorylation of AR on serine 213 (S213) has been reported to predict poor survival, whereas phosphorylation on S308 and S791 predicts better survival in patients with prostate cancer[9]. **Potential Treatment Strategies:** Several FDA-approved drugs are available that target AR and/or the AR pathway in prostate cancer, including the AR inhibitor enzalutamide, the anti-androgens flutamide and nilutamide, the luteinizing hormone-releasing hormone (LHRH) agonists leuprolide and triptorelin, and the LHRH antagonist degarelix[10,11]. The AR inhibitor cyproterone has been approved for use in prostate cancer in Canada and the UK. One approved drug, abiraterone, as well as other candidate drugs in clinical trials, specifically target CRPC[12,13]. The therapies bicalutamide and goserelin are also FDA approved for the treatment of prostate cancer and are currently under clinical investigation in breast carcinoma[11,14,15]. 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 truncated AR splice isoforms with constitutive activity, and extragonadal synthesis of androgenic compounds[16,17,18,19,20]. Therapies that target AR nuclear translocation and degradation pathways are in clinical and preclinical development in prostate cancer[21,22,23,24,25]. AR has been shown in vitro to bind to BRD4; disruption of this interaction with bromodomain and extraterminal (BET) inhibitors suppressed AR-mediated transcription and tumor growth in a preclinical model of castrate-resistant prostate cancer[26]. AR signaling may promote radioresistance in prostate cancer by transcriptionally upregulating DNA repair genes[27]. 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[28].
● ***RET*** amplification	**Gene and Alteration:** RET (rearranged during transfection) is a receptor tyrosine kinase, primarily expressed in cells of the nervous system. It has been identified as a proto-oncogene that results in transformation of cells upon recombination with a partner gene[29]. RET amplification has been reported in cancer[30], and has been associated with responses to therapies that target RET[31,32]. **Frequency and Prognosis:** Amplification or deletion of RET has been reported in 0.6-1.4% of prostate adenocarcinomas (cBioPortal, Feb 2016), although the effects of RET activation in prostate carcinoma have not been studied in detail (PubMed, Feb 2016). RET activity in prostate cancer may be indicative of small cell neuroendocrine carcinoma[33]. Ret protein overexpression has been reported in both high-grade prostate intraepithelial neoplasia (PIN) and in prostate carcinomas as compared to normal prostate tissue; the authors of the study suggest that Ret may be involved with cell growth in prostate tumors[34].

GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: Several RET inhibitors are approved by the FDA in various indications, including ponatinib, sunitinib, vandetanib, cabozantinib, lenvatinib, regorafenib, and sorafenib. Twenty three patients with RET-rearranged NSCLC treated with cabozantinib achieved 7 partial responses, 2 unconfirmed partial responses and 12 additional stable disease outcomes (Drilon et al., 2015; ASCO Abstract 8007)[35,36,37,38] and four patients with tumors harboring RET fusions (three with lung cancer and one with papillary thyroid carcinoma) benefited from vandetanib-containing therapy[39,40,41,42]. Additionally, a case study reported an exceptional response to sunitinib in a patient with a RET-amplified germ cell tumor[31]. Treatment of RET-amplified tongue adenocarcinoma with sorafenib resulted in disease stabilization lasting four months; additional treatment with sorafenib and sulindac provided disease stabilization for an additional three months[32]. Lenvatinib is FDA approved for the treatment of locally recurrent or metastatic, progressive, radioiodine-refractory differentiated thyroid cancer (DTC)[43] and, in combination with everolimus, for the treatment of advanced renal cell carcinoma following prior antiangiogenic therapy[44]. In a Phase 2 trial, lenvatinib benefited patients with medullary thyroid carcinoma and RET mutations (6 PR, 8 SD, 1 PD), as well as those without detected RET mutations (3 PR, 2 SD, 2 PD), with a trend for higher progression-free survival for patients with RET mutations (Schlumberger et al., 2012; ASCO Abstract 5591). Preclinical studies demonstrated that cells transformed by KIF5B-RET are sensitive to treatment with vandetanib, sorafenib, ponatinib, sunitinib, cabozantinib, and lenvatinib (Gozgit et al., 2013; AACR Abstract 2084)[35,45,46,47,48]. Additional preclinical studies reported that lung cancer cell lines containing a CCDC6-RET fusion were sensitive to vandetanib[49] and lenvatinib[48]. These agents and other drugs targeting RET are in clinical trials for patients with various solid tumors (Hellerstedt, 2012; ASCO Abstract 7514).
● ***TP53*** I162N	**Gene and Alteration:** Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[50]. Mutations affecting the DNA binding domain (aa 100-292), the tetramerization domain (aa 325-356), or the C-terminal regulatory domain (aa 356-393), such as observed here, are thought to disrupt the transactivation of p53-dependent genes and are predicted to promote tumorigenesis[51,52,53,54]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[55,56,57,58,59,60]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[61] to 1:20,000[60], and in the appropriate clinical context, germline testing of TP53 is recommended. **Frequency and Prognosis:** TP53 mutations have been reported in 18-40% of prostate cancers[62,63]. p53 expression has been reported to be significantly more common in late-stage and hormone-refractory prostate cancers and has been found to be associated with prostate-specific antigen (PSA) recurrence in low- and intermediate-grade prostate cancer[64]. TP53 loss has been found to be associated with prostate cancer-specific mortality in univariate analysis[65].

GENE ALTERATION	INTERPRETATION

Potential Treatment Strategies: 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 AZD1775[66,67,68,69], therapies that reactivate mutant p53 such as APR-246[70], or p53 gene therapy and immunotherapeutics such as SGT-53[71,72,73,74] and ALT-801 (Hajdenberg et al., 2012; ASCO Abstract e15010). Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer (Oza et al., 2015; ASCO Abstract 5506). Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel (Leijen et al., 2015; ASCO Abstract 2507). In a Phase 1 clinical trial, 8 of 11 evaluable patients receiving SGT-53 as a single agent exhibited stable disease[75]. Clinical trials of SGT-53 in combination with chemotherapy are underway. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model[76]. Kevetrin has also been reported to activate p53 in preclinical studies and might be relevant in the context of mutant p53 (Kumar et al., 2012; AACR Abstract 2874). Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

THERAPIES

FDA-APPROVED THERAPIES IN PATIENT TUMOR TYPE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Abiraterone	**Approved Indications:** Abiraterone is an orally available CYP17 inhibitor that is FDA approved, in combination with prednisone, in metastatic castration-resistant prostate cancer (CRPC). Abiraterone blocks the synthesis of androgen by inhibiting CYP17, an enzyme involved in androgen biosynthesis[12]. **Gene Association:** AR activation or amplification may predict sensitivity to abiraterone. **Supporting Data:** Clinical studies have reported that abiraterone/prednisone combination treatment significantly improved survival of patients with metastatic CRPC, as compared to placebo/prednisone treatment[13].
Bicalutamide	**Approved Indications:** Bicalutamide is an orally available AR inhibitor that is FDA approved for use, in combination with LHRH agonists, in stage D2 metastatic prostate carcinoma. **Gene Association:** AR activation or amplification may predict sensitivity to bicalutamide. **Supporting Data:** A long-term follow-up to a Phase 3 clinical trial of bicalutamide/LHRH analog combination therapy in patients with prostate carcinoma reported significant improvement in overall survival compared with LHRH analog monotherapy[77].
Degarelix	**Approved Indications:** Degarelix is an injectable LHRH antagonist that has been approved for reducing testosterone to castrate levels in hormone-sensitive prostate cancer. **Gene Association:** AR activation or amplification may predict sensitivity to degarelix. **Supporting Data:** A Phase 3 extension trial in patients with prostate cancer reported that degarelix was associated with significantly improved progression-free survival as compared with leuprolide[78].
Enzalutamide	**Approved Indications:** Enzalutamide is an androgen receptor inhibitor that is approved to treat patients with metastatic castration-resistant prostate cancer (CRPC) who have previously received docetaxel. **Gene Association:** AR activation or amplification may predict sensitivity to enzalutamide. **Supporting Data:** A clinical trial enrolling 1199 patients with metastatic CRPC who had received prior docetaxel showed a statistically significant improvement in overall survival (18.4 and 13.6 months in the enzalutamide and placebo arms, respectively)[79].
Flutamide	**Approved Indications:** 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. **Gene Association:** AR activation or amplification may predict sensitivity to flutamide. **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%, including three complete responses and 30 partial responses[80]. A ten-year follow-up to a Phase 3 clinical trial in patients with prostate carcinoma reported that long-term androgen-deprivation therapy (flutamide/goserelin) with radiation conferred significant benefit compared with short-term androgen-deprivation therapy with radiation[81].

Goserelin	**Approved Indications:** Goserelin is a luteinizing hormone-releasing hormone analog that is FDA approved for use with flutamide in locally confined Stage B2-C prostate carcinoma, and for the palliative treatment of advanced prostate carcinoma and of advanced breast cancer in pre- and perimenopausal women. **Gene Association:** AR activation or amplification may predict sensitivity to goserelin. **Supporting Data:** A ten-year follow-up to a Phase 3 clinical trial in patients with prostate carcinoma reported that long-term androgen-deprivation therapy (flutamide/goserelin) with radiation conferred significant benefit compared with short-term androgen-deprivation therapy with radiation[81].
Leuprolide	**Approved Indications:** Leuprolide is an injectable LHRH analog that is FDA approved for use in the palliative treatment of advanced prostate carcinoma. **Gene Association:** AR activation or amplification may predict sensitivity to leuprolide. **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%, including three complete responses and 30 partial responses[80]. A Phase 3 clinical trial reported that leuprolide administration was effective at lowering testosterone concentration to castrate levels in patients with prostate cancer[82].
Nilutamide	**Approved Indications:** Nilutamide is an orally available anti-androgen that is FDA approved for use, in combination with surgical castration, in stage D2 metastatic prostate carcinoma. **Gene Association:** AR activation or amplification may predict sensitivity to nilutamide. **Supporting Data:** A study in patients with androgen-independent prostate cancer reported a decrease in PSA levels in 40% of patients receiving nilutamide[83]. Another Phase 2 study in patients with advanced prostate cancer who failed androgen ablation therapy reported initial and sustained (greater than three months) PSA responses in 64% and 29% of patients, respectively[84].
Triptorelin	**Approved Indications:** Triptorelin is an injectable LHRH analog that is FDA approved for use in the palliative treatment of advanced prostate carcinoma. **Gene Association:** AR activation or amplification may predict sensitivity to triptorelin. **Supporting Data:** A Phase 3 clinical trial reported that triptorelin administration was effective at lowering testosterone concentration to castration levels in patients with prostate cancer[85].

ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Cabozantinib	**Approved Indications:** Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved to treat advanced renal cell carcinoma (RCC), after prior anti-angiogenic therapy, and progressive, metastatic medullary thyroid cancer (MTC). **Gene Association:** RET amplification may predict sensitivity to cabozantinib. **Supporting Data:** Phase 2 studies of cabozantinib in patients with metastatic castration-resistant prostate cancer reported clinically meaningful activity and reduced morbidity, with an objective response rate of 5% and stable disease in 75% of patients. Median progression-free survival was 24 weeks with cabozantinib and 6 weeks with placebo, the median overall survival was 11 months in the expansion cohorts[86,87].

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Lenvatinib	**Approved Indications:** Lenvatinib targets several kinases, including the VEGFRs, FGFRs, PDGFRs, RET, and KIT. It is FDA approved to treat locally recurrent or metastatic, radioiodine-refractory differentiated thyroid cancer and, in combination with everolimus, for the treatment of advanced renal cell carcinoma following prior antiangiogenic therapy. **Gene Association:** Activating mutations, fusions, or amplification of RET can increase signaling through this receptor and may predict sensitivity to lenvatinib[48,88]. Lenvatinib benefited patients with medullary thyroid carcinoma and RET mutations (6 PR, 8 SD, 1 PD), as well as patients without detected RET mutations (3 PR, 2 SD, 2 PD), with a trend for higher progression-free survival (PFS) in patients with RET mutations (Schlumberger et al., 2012; ASCO Abstract 5591). **Supporting Data:** Lenvatinib has primarily been evaluated for the treatment of iodine-131-refractory, differentiated thyroid carcinoma[43] or for patients with advanced renal cell carcinoma[44]. In a Phase 1 dose-escalation study of single-agent lenvatinib for patients with advanced solid tumors, confirmed partial response (PRs) were achieved by 16% (12/77) and unconfirmed PRs by an additional 4% (3/77) of patients; stable disease (SD) was achieved by both of the participants with prostate carcinoma[89]. The combination of lenvatinib and golvatinib, in a Phase 1b trial for the treatment of advanced solid tumors, resulted in PRs for 5/14 of patients, including 2 with prostate cancer; an additional 13/24 patients experienced SD (Kwak et al., 2014; ANE Abstract 484). Lenvatinib benefited patients with medullary thyroid carcinoma and RET mutations (6 PR, 8 SD, 1 PD) as well as patients without detected RET mutations (3 PR, 2 SD, 2 PD), with a trend for higher PFS for patients with RET mutations (Schlumberger et al., 2012; ASCO Abstract 5591); 2 patients with MTC and dual PIK3CA and RET mutations experienced PRs in response to lenvatinib[90].
Ponatinib	**Approved Indications:** Ponatinib is a multikinase inhibitor targeting BCR-ABL, RET, KIT, FLT-3, PDGFRs, VEGFRs, FGFRs, and other tyrosine kinases. It is FDA approved for the treatment of advanced, T315I-mutated chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), as well as for CML and Ph+ ALL patients for whom no other tyrosine kinase inhibitor is indicated. **Gene Association:** Ponatinib has been shown to potently inhibit overexpression or activated forms of RET kinase, both point mutations and fusions, in preclinical studies of medullary thyroid carcinoma and NSCLC cell lines (Gozgit et al., 2013; AACR abstract 2084)[91,92]. **Supporting Data:** Ponatinib has not been extensively studied in the context of prostate cancer (PubMed, Feb 2016). Ponatinib has shown efficacy in preclinical models of endometrial, bladder, gastric, breast, lung, colon, and medullary thyroid carcinomas, and is being clinically tested in some solid tumor types including NSCLC (Gozgit et al., 2013; AACR Abstract 2084)[93].
Regorafenib	**Approved Indications:** Regorafenib is a small-molecule inhibitor of multiple kinases, including RET, VEGFRs, PDGFRs, KIT, and RAF family proteins[94]. It is FDA approved for the treatment of metastatic colorectal cancer (CRC) or advanced gastrointestinal stromal tumors (GIST)[95,96,97]. **Gene Association:** RET amplification may predict sensitivity to regorafenib. **Supporting Data:** Regorafenib has primarily been studied as a treatment for CRC and GIST, and data are limited for other tumor types. Regorafenib improved overall survival in patients with CRC and progression-free survival in patients with imatinib/sunitinib-refractory GIST as compared with placebo[95,96]. A Phase 1 trial of regorafenib in 47 patients with solid tumors reported 3 (6%) partial responses in patients with CRC, renal cell carcinoma, or osteosarcoma[98]. A Phase 1 trial of regorafenib in 17 patients with refractory non-small cell lung cancer (NSCLC) reported stable disease lasting longer than 12 weeks in 4 (23%) patients (Kies et al., 2010; ASCO Abstract 7585). Regorafenib use has been linked to the development of intestinal perforation in 2 patients[99].

Sorafenib	**Approved Indications:** Sorafenib is a kinase inhibitor that targets the RAF kinases, KIT, FLT3, RET, VEGFRs, and PDGFRs. It is FDA approved for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and recurrent or metastatic differentiated thyroid carcinoma. **Gene Association:** Kinase inhibitors targeting RET, such as sorafenib, may be relevant in a tumor harboring RET amplification. **Supporting Data:** Sorafenib is under clinical investigation in multiple tumor types. Results of five Phase 2 clinical trials of sorafenib in patients with hormone-refractory prostate cancer reported a relatively short progression-free survival, but outcomes in terms of overall survival and quality of life were promising (Zaborowska et al. 2012; 22852011). A Phase 1 study of imatinib in combination with sorafenib in patients with refractory castration-resistant prostate cancer reported no biochemical responses but stable disease in two patients[100]. A Phase 2 study of sorafenib and bicalutamide in 39 patients with castration-resistant prostate cancer (CRPC) observed a PSA response or stable disease lasting 6 months or longer in 47% (18/39) of cases[101]. Another Phase 2 study of single agent sorafenib as second-line treatment for CRPC reported moderate activity (3.7 months progression free survival and 18.0 months overall survival)[102].
Sunitinib	**Approved Indications:** Sunitinib is a small-molecule tyrosine kinase inhibitor that targets PDGFRs, VEGFRs, KIT, FLT3, CSF-1R, and RET. It is FDA approved for the treatment of advanced renal cell carcinoma, advanced or metastatic pancreatic neuroendocrine tumors, and gastrointestinal stromal tumors (GIST) after progression on imatinib. **Gene Association:** Amplification of RET may predict sensitivity to tyrosine kinase inhibitors such as sunitinib. In one study, a patient with metastatic germ cell tumor harboring a RET amplification had a response to sunitinib[31]. **Supporting Data:** A Phase 2 study of sunitinib in metastatic castration-resistant prostate cancer reported one partial response and two PSA responses. Among 25 patients with baseline bone metastases, five partial and one complete bone scan responses were recorded[103]. In a Phase 1/2 trial of sunitinib and stereotactic body radiation therapy in patients with various metastatic solid tumors, patients with kidney and prostate primary tumors had significantly improved overall survival[104]. A Phase 1 study of sunitinib in combination with androgen deprivation therapy and external-beam intensity modulated radiation therapy in men with localized high-risk prostate cancer showed toxicity at initial doses of sunitinib, but the combination was deemed feasible at lower doses[105].
Vandetanib	**Approved Indications:** Vandetanib is a multikinase inhibitor that targets RET, VEGFRs, SRC family kinases, and EGFR. It is FDA approved for the treatment of medullary thyroid cancer (MTC). **Gene Association:** Kinase inhibitors targeting RET, such as vandetanib, may be relevant in a tumor harboring RET amplification[91]. **Supporting Data:** A Phase 2 study of vandetanib in combination with docetaxel and prednisolone in 86 patients with metastatic hormone-refractory prostate cancer reported that the vandetinib group had fewer PSA responses and more progression events compared to placebo plus docetaxel and prednisolone[106]. In preclinical studies, vandetinib inhibited growth of several xenograft tumors, including prostate tumors[107].

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CLINICAL TRIALS TO CONSIDER

IMPORTANT: 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 meant to be a complete list of available trials. In order to conduct a more thorough search, please go to www.clinicaltrials.gov and use the search terms provided below. For more information about a specific clinical trial, type the NCT ID of the trial indicated below into the search bar.

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***AR*** amplification	Tumors with AR amplification or activation may be responsive to therapies that inhibit the androgen receptor. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "AR", "abiraterone", "bicalutamide", "degarelix", "enzalutamide", "flutamide", "goserelin", "leuprolide", "nilutamide", "triptorelin", "ARN-509", "EPI-506", "prostate carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men With Biochemically Relapsed Hormone Sensitive Prostate Cancer	Phase 1/Phase 2	AR	Arizona, California, Illinois, Oregon, Washington	NCT01790126
Phase II Trial of Enzalutamide for Castrate-resistant Prostate Cancer (CRPC) With Correlative Assessment of Androgen Receptor (AR) Signaling and Whole-exome and Transcriptome Sequencing	Phase 2	AR	Massachusetts, Washington	NCT01942837
Phase 1b Study of ARN 509 Plus Everolimus in Men With Progressive Metastatic Castration-Resistant Prostate Cancer After Treatment With Abiraterone Acetate	Phase 1	AR, mTOR	New York	NCT02106507
Addition of Pembrolizumab Upon Progression on Enzalutamide in Men With mCRPC	Phase 2	PD-1, AR	Maryland, Oregon	NCT02312557
A Phase 1/2 Open-Label Study to Assess the Safety, Pharmacokinetics, and Anti-Tumor Activity of Oral EPI-506 in Patients With Metastatic Castration-Resistant Prostate Cancer	Phase 1/Phase 2	AR	Arizona, Michigan, Washington, British Columbia (Canada)	NCT02606123

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***RET*** amplification	RET amplification, as well as RET activating mutations and fusions, may confer sensitivity to kinase inhibitors targeting RET. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "RET", "vandetanib", "sorafenib", "sunitinib", "ponatinib", "regorafenib", "cabozantinib", "lenvatinib", "XL184", "prostate carcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase I Trial of Riluzole and Sorafenib in Patients With Advanced Solid Tumors and Melanoma	Phase 1	FLT3, KIT, PDGFRs, RAFs, RET, VEGFRs, CSF1R	New Jersey	NCT01303341
Phase II Randomized Study of Docetaxel With or Without Low-dose, Short Course Sunitinib in the Treatment of Advanced Solid Tumors	Phase 2	VEGFRs, PDGFRs, KIT, FLT3, CSF1R, RET	Singapore (Singapore)	NCT01803503
A Phase I Study To Evaluate The Safety, Pharmacokinetics And Pharmacodynamics Of Escalating Doses Of A Vaccine-based Immunotherapy Regimen (Vbir) For Prostate Cancer (Pf-06753512)	Phase 1	CTLA-4, CSF-1R, FLT3, KIT, RET, PDGFRs, VEGFRs	Nebraska, Nevada, New York, Washington	NCT02616185
Phase II Study of Ponatinib for Advanced Cancers With Genomic Alterations in Fibroblastic Growth Factor Receptor (FGFR) and Other Genomic Targets (KIT, PDGFRá, RET FLT3, ABL1)	Phase 2	BCR-ABL, RET, KIT, FLT-3, PDGFRs, VEGFRs, FGFRs	Michigan, Ohio	NCT02272998

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 make their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ABL2 amplification	***ALK*** R209C	***ATM*** L2890I	***CDC73*** amplification	***DDR2*** amplification	***DICER1*** S295C
FANCE P18S	***FGFR2*** E146G	***HSD3B1*** amplification	***LYN*** amplification	***MCL1*** amplification	***MLL2*** G4373S
NOTCH2 amplification	***PARK2*** M1T,R334C	***PDGFRA*** R979H	***PREX2*** amplification	***PRKDC*** amplification	***RAD50*** R884H
RUNX1T1 amplification	***SETD2*** T1033A	***TOP2A*** R1218K			

APPENDIX

GENES ASSAYED IN FOUNDATIONONE

FoundationOne is designed to include all 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 315 genes as well as introns of 28 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	*ABL2*	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B)*	*APC*	*AR*
ARAF	*ARFRP1*	*ARID1A*	*ARID1B*	*ARID2*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*	*BCOR*
BCORL1	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTK*	*C11orf30 (EMSY)*
CARD11	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CD274*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHD2*	*CHD4*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CRLF2*
CSF1R	*CTCF*	*CTNNA1*	*CTNNB1*	*CUL3*	*CYLD*	*DAXX*	*DDR2*	*DICER1*	*DNMT3A*
DOT1L	*EGFR*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*
ERG	*ERRFI1*	*ESR1*	*EZH2*	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*
FANCG	*FANCL*	*FAS*	*FAT1*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*	*FH*	*FLCN*	*FLT1*	*FLT3*
FLT4	*FOXL2*	*FOXP1*	*FRS2*	*FUBP1*	*GABRA6*	*GATA1*	*GATA2*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GLI1*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GRM3*
GSK3B	*H3F3A*	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*HSP90AA1*	*IDH1*	*IDH2*	*IGF1R*
IGF2	*IKBKE*	*IKZF1*	*IL7R*	*INHBA*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*
JAK2	*JAK3*	*JUN*	*KAT6A (MYST3)*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*
KIT	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*	*LMO1*	*LRP1B*	*LYN*	*LZTR1*
MAGI2	*MAP2K1*	*MAP2K2*	*MAP2K4*	*MAP3K1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*
MEN1	*MET*	*MITF*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH6*	*MTOR*	*MUTYH*
MYC	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*
NOTCH2	*NOTCH3*	*NPM1*	*NRAS*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*	*PAK3*
PALB2	*PARK2*	*PAX5*	*PBRM1*	*PDCD1LG2*	*PDGFRA*	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3CA*
PIK3CB	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PLCG2*	*PMS2*	*POLD1*	*POLE*	*PPP2R1A*	*PRDM1*
PREX2	*PRKAR1A*	*PRKCI*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*	*QKI*	*RAC1*
RAD50	*RAD51*	*RAF1*	*RANBP2*	*RARA*	*RB1*	*RBM10*	*RET*	*RICTOR*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*RUNX1T1*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SLIT2	*SMAD2*	*SMAD3*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX10*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SPTA1*	*SRC*	*STAG2*	*STAT3*	*STAT4*	*STK11*
SUFU	*SYK*	*TAF1*	*TBX3*	*TERC*	*TERT (promoter only)*	*TET2*	*TGFBR2*	*TNFAIP3*	*TNFRSF14*
TOP1	*TOP2A*	*TP53*	*TSC1*	*TSC2*	*TSHR*	*U2AF1*	*VEGFA*	*VHL*	*WISP3*
WT1	*XPO1*	*ZBTB2*	*ZNF217*	*ZNF703*					

DNA Gene List: For the Detection Select Rearrangements

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*EGFR*	*ETV1*	*ETV4*
ETV5	*ETV6*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*MSH2*	*MYB*	*MYC*	*NOTCH2*
NTRK1	*NTRK2*	*PDGFRA*	*RAF1*	*RARA*	*RET*	*ROS1*	*TMPRSS2*		

For more comprehensive information please log on to the Interactive Cancer Explorer™
To set up your Interactive Cancer Explorer account, contact your sales representative or call (888) 988-3639.

APPENDIX

FOUNDATIONONE PERFORMANCE SPECIFICATIONS

ACCURACY		
Sensitivity: Base Substitutions	At Mutant Allele Frequency ≥10%	>99.9% (CI* 99.6%-100%)
	At Mutant Allele Frequency 5-10%	99.3% (CI* 98.3%-99.8%)
Sensitivity: Insertions/Deletions (1-40 bp)	At Mutant Allele Frequency ≥20%	97.9% (CI* 92.5%-99.7%)
	At Mutant Allele Frequency 10-20%	97.3% (CI* 90.5%-99.7%)
Sensitivity: Copy Number Alterations—Amplifications (ploidy <4, Amplification with Copy Number ≥8)	At ≥30% tumor nuclei	>99.0% (CI* 93.6%-100%)
	At 20% tumor nuclei	92.6% (CI* 66.1%-99.8%)
Sensitivity: Copy Number Alterations—Deletions (ploidy <4, Homozygous Deletions)	At ≥30% tumor nuclei	97.2% (CI* 85.5%-99.9%)
	At 20% tumor nuclei	88.9% (CI* 51.8%-99.7%)
Sensitivity: Rearrangements (selected rearrangements in specimens with ≥20% tumor nuclei)**		>90.0% [1] >99.0% for ALK fusion[2] (CI* 89.1%-100%)
Specificity of all variant types	Positive Predictive Value (PPV)	>99.0%
REPRODUCIBILITY (average concordance between replicates)		96.4% inter-batch precision 98.9% intra-batch precision

*95% Confidence Interval

** Performance for gene fusions within targeted introns only. Sensitivity for gene fusions occurring outside targeted introns or in highly repetitive intronic sequence contexts is reduced.

[1] Based on analysis of coverage and re-arrangement structure in the COSMIC database for the solid tumor fusion genes where alteration prevalence could be established, complemented by detection of exemplar rearrangements in cell line titration experiments.

[2] Based on ALK re-arrangement concordance analysis vs. a standard clinical FISH assay described in: Yelensky, R. et al. Analytical validation of solid tumor fusion gene detection in a comprehensive NGS-based clinical cancer genomic test, In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract nr 4699

Assay specifications were determined for typical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne, please refer to the article, Frampton, GM. et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing, Nat Biotechnol (2013 Oct. 20).

For additional information specific to the performance of this specimen, please contact Foundation Medicine, Inc. at 1-888-988-3639.

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APPENDIX

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APPENDIX

ABOUT FOUNDATIONONE™

FoundationOne™: FoundationOne was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

Diagnostic Significance: FoundationOne identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test 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 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 for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne 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 analytical methodology has identified as being present in <10% of the assayed tumor DNA.

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.

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.

Alterations and Drugs Not Presented in Ranked Order: In this Report, neither any biomarker alteration, nor any drug associated with potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

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.

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. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne is performed using DNA derived from tumor, and as such germline events may not be reported. The following targets typically have low coverage resulting in a reduction in sensitivity: *SDHD* exon 6 and *TP53* exon 1.

FoundationOne complies with all European Union (EU) requirements of the IVD Directive 98/79EC. As such, the FoundationOne Assay has been registered for CE mark by our EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

For more comprehensive information please log on to the Interactive Cancer Explorer™
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