PATIENT
DISEASE
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

NO REPORTABLE ALTERATIONS WITH COMPANION DIAGNOSTIC (CDx) CLAIMS

See professional services section for additional information

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 53 Muts/Mb §
ATRX E259*
CASP8 E36*
FBXW7 R465C
FH splice site 1237-1G>T
HSD3B1 T353M
KDM5C E448*
MSH6 E908*
MSH6 E1023*
NT5C2 R367Q
PIK3CA R88Q
PIK3CA M1043I
POLE A456P
PTEN E7*
PTEN S179I
PTEN F341V
RB1 E323*
TP53 S127F
TP53 Y327*

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result 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. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

TABLE 1

INDICATIONS	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), 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)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E or 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)
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	Rubraca® (Rucaparib)

ABOUT THE TEST FoundationOne CDx™ is the first FDA-approved broad companion diagnostic for 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

Tumor Mutational Burden - TMB-High (53 Muts/Mb)
Microsatellite Status - MS-Stable

Genomic Findings

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

FBXW7 R465C
PIK3CA M1043I, R88Q
PTEN E7*, F341V, S179I
ATRX E259*
CASP8 E36*
FH splice site 1237-1G>T
HSD3B1 T353M
KDM5C E448*
MSH6 E1023*, E908*
NT5C2 R367Q
POLE A456P
RB1 E323*
TP53 S127F, Y327*

7 Therapies with Clinical Benefit
0 Therapies with Lack of Response
32 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - TMB-High (53 Muts/Mb)	none	Atezolizumab
		Avelumab
		Durvalumab
		Nivolumab
10 Trials *see p. 17*		Pembrolizumab
Microsatellite status - MS-Stable	**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)
FBXW7 - R465C	none	Everolimus
10 Trials *see p. 19*		Temsirolimus
PIK3CA - M1043I, R88Q	none	Everolimus
10 Trials *see p. 21*		Temsirolimus
PTEN - E7*, F341V, S179I	none	Everolimus
14 Trials *see p. 23*		Temsirolimus

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 Alterations section.

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
Tumor Mutational Burden

CATEGORY
TMB-High (53 Muts/Mb)

POTENTIAL TREATMENT STRATEGIES

On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4[1], anti-PD-L1[2-4], and anti-PD-1 therapies[5-7]; FDA-approved agents include ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) in patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19)[5]. In studies of patients with either NSCLC or colorectal cancer (CRC), patients whose tumors harbor elevated mutational burden reported higher overall response rates to pembrolizumab[5-7]. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses following treatment with pembrolizumab[8] or nivolumab[9], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab[10], and two pediatric patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab[11]. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab[1,12] and anti-PD-1/anti-PD-L1 treatments[3]. For patients with metastatic urothelial carcinoma, those who responded to atezolizumab treatment had a significantly increased mutational load [12.4 mutations (mut) per megabase (Mb)] compared to nonresponders (6.4 mut/Mb)[2], and mutational load of 16 mut/Mb or higher was associated with significantly longer overall survival[4].

FREQUENCY & PROGNOSIS

Uterine carcinosarcoma harbors a median TMB of 3.6 mutations per megabase (muts/Mb), and 3.3% of cases have high TMB (>20 muts/Mb)[13]. In one study of 22 gynecologic carcinosarcomas, the average mutation burden was 1.4 muts/Mb; the four tumors with mutation in either MLH1 or MSH6 had the highest mutation burden in this study ranging from 29-191 muts/Mb[14]. Low TMB has been reported in 65% of cases in the TCGA Uterine Corpus Endometrioid Carcinoma dataset[15]; another study evaluating TMB in endometrial adenocarcinomas reported that 76% of tumors had a mutational burden of 0-10.3 muts/Mb[16]. Low mutation rate in endometrial carcinomas is associated with poorer prognosis[15].

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[17-18] and cigarette smoke in lung cancer[5,19], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[15,20-23], and microsatellite instability (MSI)[15,22-23]. The tumor seen here harbors a high TMB. This type of mutation load has been shown to be associated with sensitivity to immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma[1], anti-PD-L1 therapy in urothelial carcinoma[2], and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer[5-6], potentially due to expression of immune-reactive neoantigens in these tumors[5].

BIOMARKER
Microsatellite status

CATEGORY
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[24-26], including approved therapies nivolumab and pembrolizumab[6,27]. 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)[28]. Pembrolizumab therapy resulted in a significantly lower objective response rate (ORR) in MSS colorectal cancer (CRC) compared with MSI-H CRC (0% vs. 40%)[6]. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with MSI-H tumors than those without[27].

FREQUENCY & PROGNOSIS

MSI has been reported in 5-23% of uterine carcinosarcomas, although the prognostic significance of MSI status in this context has not been established[29-34]. In endometrial cancers in general, MSI has been reported in 16-33% of cases[35-43] and is associated more frequently with the endometrioid type[36,39-40], advanced stage[36,40-44], and myometrial invasion[40-41,44]. Data regarding the role of high MSI on prognosis and survival in endometrial cancer are conflicting, with most studies finding no relationship between MSI-H endometrial cancers and survival[36,39,42,44-46], and one study predicting improved disease-free and disease-specific survival[40]. However, these studies often evaluated endometrial cancers of all FIGO stages together. Studies specifically analyzing early stage endometrial cancer have reported a correlation between MSI-H and decreased survival[38,41,43,46], thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

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[47]. 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[47-49]. The tumor seen here is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[50-52]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[47,49,51-52].

GENE
FBXW7

ALTERATION
R465C

POTENTIAL TREATMENT STRATEGIES

Preclinical studies indicate that loss or inactivation of FBXW7 may predict sensitivity to mTOR inhibitors, such as the FDA-approved therapies everolimus and temsirolimus[53-54]. In two case reports, temsirolimus elicited a radiographic response in a patient with FBXW7-mutant lung cancer[55], and a patient with FBXW7-mutated papillary renal cell carcinoma responded to everolimus for 13 months[56]. In another study, 7/10 patients with FBXW7 mutations in different tumor types achieved stable disease for 2.2-6.8+ months upon treatment with various mTOR inhibitors[57]. Reduction in FBXW7 was reported to result in accumulation of the FBXW7 substrates NOTCH1, c-MYC, and cyclin E[58], but therapeutic strategies targeting these proteins have not been tested in the context of FBXW7 inactivation[59-6667]. FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[68].

FREQUENCY & PROGNOSIS

FBXW7 mutations have been found in 39% (22/56) of cases in the Uterine Carcinosarcoma TCGA dataset (cBioPortal, Mar 2017). Studies have variously reported FBXW7 mutation in 12% of uterine carcinosarcomas, 18-29% of uterine serous carcinomas, 16% of endometrial cancers, and 2% of endometrioid endometrial cancers[69-74]. In primary endometrial carcinomas, FBXW7 mutations were found to be correlated with lymph node involvement[75].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[76]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[76-77]. Alterations that disrupt the dimerization domain (aa67-90)[78-79], F-box domain (aa278-324)[80], or WD40 repeats (aa378-659)[81], including hot spot residues R465, R479, or R505, are likely to result in failure to target its substrates for degradation and to promote tumorigenesis[77,82-84].

GENE
PIK3CA

ALTERATION
M1043I, R88Q

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K or AKT[85-8687]. On the basis of clinical benefit for patients with PIK3CA mutations and preclinical evidence, PIK3CA-mutated tumors may also respond to mTOR inhibitors, including everolimus and temsirolimus[88-93]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control at the recommended Phase 2 dose (3/14 partial responses [PRs], 8/14 stable disease)[94]. The pan-PI3K inhibitor buparlisib has shown limited activity as monotherapy against PIK3CA-mutated tumors[95-98]. PI3K-alpha-selective inhibitors, such as alpelisib, may have a bigger therapeutic window than pan-PI3K inhibitors[87,99]. Alpelisib achieved PRs for 11% of patients with PIK3CA-mutated advanced solid tumors[85]. A Phase 1 study of the pan-AKT inhibitor AZD5363 observed responses for 3/15 and 1/14 patients with PIK3CA-mutated breast cancer or other gynecological malignancies, respectively[86]. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in tumors with ERBB2 amplification and PIK3CA mutation[89,100-103].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 27% (15/56) of gynecologic carcinosarcoma samples analyzed in one study[14]. In another study, sequencing of PIK3CA exons 9 and 20 in 37 uterine carcinosarcoma samples identified PIK3CA mutation in a single case (2.7% of samples)[104]. Another study reported PIK3CA mutations in 19% of gynecologic carcinosarcoma tumors, and the presence of both PIK3CA and RAS mutations has been reported as both a signature of uterine origin and indicator of poor patient prognosis[105].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[106-107]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[108-124].

GENE
PTEN

ALTERATION
E7*, F341V, S179I

POTENTIAL TREATMENT STRATEGIES

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[125-129] such as the mTOR inhibitors temsirolimus and everolimus or the PI3K inhibitor copanlisib. Other inhibitors of mTOR, PI3K, and AKT are also in clinical trials. Preclinical studies suggest that PTEN-deficient cancers, in the absence of other oncogenic mutations, depend primarily on the beta isoform of PI3K (PI3K-beta)[130-132]; PI3K-beta-specific inhibitors are in clinical trials for PTEN-deficient tumors. In the context of concurrent PIK3CA mutation, PTEN loss may predict resistance to PI3K-alpha-specific inhibitors[87,133]. Loss of PTEN expression may also contribute to trastuzumab resistance in patients with breast cancer[134-135]. Emerging clinical and preclinical data suggest that PTEN alterations may predict sensitivity to PARP inhibitors. Four patients with tumors harboring PTEN mutation or loss, but no detected BRCA1/2 alterations, experienced clinical benefit from PARP inhibition by olaparib or niraparib[136-138]. However, although multiple preclinical studies have demonstrated sensitivity of PTEN-mutant cell lines to various PARP inhibitors[137,139-142], other studies have observed a lack of association between PTEN mutation and PARP inhibitor sensitivity[142-143]; PTEN association with sensitivity to PARP inhibitors may depend on the cell type or context.

FREQUENCY & PROGNOSIS

A study of gynecological carcinosarcomas, including 17 uterine cases and 5 ovarian cases, identified alterations activating the PI3K pathway in over half of the samples analyzed, including PTEN mutations in 41% (9/22) of cases[14]. PTEN mutation has been associated with endometrioid-type but not serous-type uterine carcinosarcomas, and was detected in 17% (3/18) of endometrioid-type uterine carcinosarcomas in one study[144-145]. Loss of PTEN expression has been reported in 39% (12/31) of primary uterine carcinosarcomas, and specifically in 64% (20/37) of the epithelial component and 47% (17/33) of the mesenchymal component[146]. In addition, loss of PTEN expression has also been found in 53% (10/17) of the epithelial component of metastatic tissue of uterine carcinosarcomas, but not in any of the five mesenchymal components studied[146].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[125]. PTEN alterations that disrupt the N-terminal PIP2 binding motif[147], the phosphatase domain (amino acids 14-185)[148-174], the C2 domain (amino acids 190-350)[148,150,160,175-181], the C-terminal region[182-183], and/or PTEN localization[184], such as observed here, are predicted to cause a loss of function. Although other alterations also seen here have not been fully characterized and their effect on PTEN function is unclear, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance. Mutations in PTEN underlie several inherited disorders collectively termed PTEN hamartoma tumor syndrome (PHTS), which includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[185-186]. The mutation rate for PTEN in these disorders ranges from 20-85% of patients. The estimated incidence of Cowden syndrome is approximately 1:200,000, but it is widely believed that this may be an underestimate[185,187]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context germline testing for mutations affecting PTEN is recommended.

GENE
ATRX

ALTERATION
E259*

POTENTIAL TREATMENT STRATEGIES

No targeted therapies are available to address ATRX inactivation. Although ATR inhibition is being investigated as a potential therapeutic approach in the context of ATL, a preclinical study demonstrated that ATRX inactivation is not sufficient to confer sensitivity to ATR inhibitors[188]. However, ATRX-deficient GBM cells were sensitive to double-strand break-inducing agents doxorubicin, irinotecan, and topotecan, but not single-strand break-inducing agents such as temozolomide[189]. Preclinical evidence suggests that ATRX may be required for CDK4/6 inhibitors to be most effective[190].

FREQUENCY & PROGNOSIS

ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)[191-193], 12.6% of pheochromocytomas and paragangliomas[194], and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma[195-199]. ATRX loss in PNET[191,200] and melanoma[201] and mutation in other neuroendocrine tumors[194] is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy[189]. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma[202-205] and has been proposed as a distinguishing biomarker[203-205]. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma[196-199]. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with IDH1/2 mutation but no ATRX mutation[203]. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS[206-207].

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance[208-209]. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)[192,207,210-211]; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors[188,208]. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[212].

GENE
CASP8

ALTERATION
E36*

POTENTIAL TREATMENT STRATEGIES
There are no targeted approaches to address alterations in CASP8. Inhibitors of caspase-8 have been used in cancer models[213-214], and may be beneficial in certain contexts. However, this remains to be tested clinically.

FREQUENCY & PROGNOSIS
CASP8 mutations have been observed in 8-9% of head and neck squamous cell carcinoma (HNSCC)[215-217], 5% of colorectal[218], 4% of cervical[219] and 3% of breast[220] carcinoma cases; mutations in HNSCC have been correlated with improved outcome[221]. Loss of CASP8 expression is frequently observed in neuroblastoma, predominantly due to hypermethylation[222], although deletions are also seen[223-226]. Loss of CASP8 expression in neuroblastoma has been implicated in promoting metastasis[227], recapitulated in a MYCN-driven mouse model of neuroblastoma[228], although there are conflicting reports regarding the prognostic impact of CASP8[223,226,229]. CASP8 hypermethylation and reduction of expression are also frequent in medulloblastoma[230-233], although impact on prognosis is unclear[231,233]. Conversely, CASP8 overexpression has been noted in acute myeloid leukemia (AML)[234], cervical cancer[235], hepatocellular carcinoma (HCC)[236], non-small cell lung cancer (NSCLC)[237], and myeloproliferative neoplasms (MPNs)[238]. The prognostic significance of CASP8 expression may depend on cancer type or context. Hypermethylation and/or reduced expression of CASP8 has been associated with poor prognosis in ovarian cancer[239], prostate cancer[240], and B-ALL[241], but has been reported to be a good prognostic marker in cervical squamous cell carcinoma[242]; moreover, CASP8 overexpression has been reported to be a poor prognostic factor in HCC[236] and NSCLC[237]. Germline SNPs in CASP8 have been correlated with prognosis and/or clinicopathological features in breast[243-245], small cell lung[246], prostate[247], and gastric[248] cancers, renal cell carcinoma[249-250], and MYCN-amplified neuroblastoma[251]. SNPs in CASP8 have also been correlated with survival in patients who have undergone an allogeneic stem cell transplantation following alemtuzumab-mediated T-cell depletion[252] and in patients with lung adenocarcinoma treated with platinum-based chemotherapy[253].

FINDING SUMMARY
CASP8 encodes caspase-8, a multifunctional protein that mediates apoptosis[254-257], cell motility[258-259], and cell signaling, including through the NFkB[260-262] and MAPK[263-264] pathways. The role of CASP8 in cancer is complex and context-dependent, with diverse cancer types exhibiting either overexpression or loss of expression. CASP8 mutations found in the context of cancer tend to be truncating or missense mutations; the majority of the characterized mutations impair apoptosis[215,218,265-266](Mandruzzato et al., 1997 9271594) and promote NFkB activation[267]. Germline polymorphisms in CASP8, including both coding and non-coding alterations, have been correlated with either reducing or increasing risk of various cancers[243,268-269] including breast[243,270-271], prostate[247,272], ovarian[273-275], renal cell[243,249-250], colorectal[243,276], gastric[277-278], esophageal[279-281], lung[271,279], cervical[243,282], bladder[243,283], and basal cell[284] carcinomas, as well as chronic lymphocytic leukemia (CLL)[285], non-Hodgdkin lymphoma[286], and B-cell acute lymphoblastic leukemia (B-ALL)[287].

GENE
FH

ALTERATION
splice site 1237-1G>T

POTENTIAL TREATMENT STRATEGIES
A preclinical study showed that FH-deficient renal cancer cells are dependent on ABL1 activity and sensitive to the multikinase inhibitor vandetanib; treatment with vandetanib inhibited the growth and tumorigenicity of these cells in vitro and in vivo[288]. Tumors with FH loss or inactivation may therefore be sensitive to vandetanib, which is FDA approved to treat medullary thyroid cancer and is in clinical trials in solid tumors. A Phase 2 trial of bevacizumab and erlotinib reported overall response rate in 60% (12/20) of patients with hereditary leiomyomatosis and renal cell cancer, and 29% (6/21) of patients with sporadic papillary renal cell carcinoma[289].

FREQUENCY & PROGNOSIS
Germline mutation of FH typically results in protein truncation or loss and is associated with familial leiomyomatosis and susceptibility to an aggressive form of renal cell carcinoma (RCC)[290]. FH-deficient RCC is associated with a metabolic shift termed the Warburg effect, characterized by the activation of aerobic glycolysis and oncogenic pathways[291-292].

FINDING SUMMARY
FH encodes fumarate hydratase, an enzymatic component of the Krebs cycle. FH has been identified as a possible hypoxia inducible factor activating gene[293].

Electronically signed by Jeff Ross, M.D. | Jeffrey Ross, M.D., Medical Director | 27 April 2018 | Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

GENE
HSD3B1

ALTERATION
T353M

POTENTIAL TREATMENT STRATEGIES
There are no therapies available to directly target genomic alterations in HSD3B1. Preclinical studies have suggested that HSD3B1 N367T may lead to resistance to androgen deprivation therapy, such as abiraterone, a drug that blocks androgen synthesis and DHT binding to AR[294-296].

FREQUENCY & PROGNOSIS
HSD3B1 mutation in cancer is rare, being observed in adenocarcinomas of the endometrium (1.2-1.3%), colon (1.3-1.4%), stomach (1.3-1.4%), and lung (0.9-1.6%); squamous cell carcinomas of the lung (0.9-2.8%) and skin (3.6-10.4%); and bladder urothelial carcinoma (0.9-1.6%), as well as in <0.5% of other cancers including prostate carcinoma (cBioPortal, COSMIC, 2017). Loss of heterozygosity and germline N367T mutation of HSD3B1 are common in castrate resistant prostate cancer[297-298], and somatic mutation has been reported in 3/25 cases with wild-type germline status[295,299].

FINDING SUMMARY
HSD3B1 encodes an enzyme that catalyzes the conversion of dehydroepiandrosterone to dihydrotestosterone (DHT), a potent androgen. The N367T mutation in HSD3B1 has been shown to block ubiquitination and degradation, thereby increasing enzyme stability and DHT levels and upregulating androgen receptor (AR) signaling[295].

GENE
KDM5C

ALTERATION
E448*

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in KDM5C.

FREQUENCY & PROGNOSIS
Somatic mutations of KDM5C have been observed in a number of solid tumors and the role of KDM5C inactivation has been well characterized in clear cell renal cell carcinoma (ccRCC)[300-303]. However, KDM5C amplification and overexpression has been implicated in prostate cancer where KDM5C has been associated with poor prognosis[304].

FINDING SUMMARY
KDM5C encodes a histone lysine demethylase that acts, along with related histone-modifying enzymes, to control gene expression in response to developmental and environmental cues[305]. In addition to its role as a histone-modifying demethylase, KDM5C has been suggested to play a role in regulation of the SMAD3 signal transduction response to TGF-beta, a role that would be consistent with function as a tumor suppressor[306]. Germline inactivating mutations in KDM5C cause an X-linked intellectual disability syndrome also characterized by short stature and hyperreflexia[307].

GENE
MSH6

ALTERATION
E1023*, E908*

POTENTIAL TREATMENT STRATEGIES
Numerous studies in various cancer types have shown that MSH6 loss or inactivation is associated with MSI and increased mutation burden[22,48,308-311]. Clinical studies have shown that MSI is associated with patient responses to anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[6,312] and nivolumab[313]. Higher mutation burden was also reported to be associated with response to pembrolizumab[5]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[24], potential biomarkers of response to PD-1 targeted immunotherapies. Therefore, inactivation of MSH6 may confer sensitivity to anti-PD-1 immune checkpoint inhibitors, which are under investigation in clinical trials.

FREQUENCY & PROGNOSIS
MSH6 alterations have been reported in 3.6% (2/56) of uterine carcinosarcoma samples analyzed in the TCGA dataset (cBioPortal, May 2017). Multiple studies have cited an increased risk (16-44%) of endometrial cancer for female carriers of germline MSH6 mutations[314-316]. In one study, MSH6 protein was absent in 5% (51/1049) of endometrial carcinomas analyzed[317]. MMR protein alterations have been associated with worse overall survival and progression-free survival in patients with endometrial tumors[318].

FINDING SUMMARY
MSH6 encodes MutS homolog 6 protein, a member of the mismatch repair (MMR) gene family. Defective MMR as a result of MSH6 mutation can result in microsatellite instability (MSI)[48]. As a component of the heterodimeric MutSalpha complex with MSH2, MSH6 mediates MutSalpha binding to defective regions of DNA, thereby triggering the DNA damage response[319]. MSH6 alterations that result in disruption or loss of the PWWP[319-321] and/or ATPase domain[322-324], such as observed here, are predicted to lead to loss of function. Germline mutations in MSH6 are associated with both 'typical' and 'atypical' forms of Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC), which accounts for 1-7% of all colorectal cancers[325]. Approximately 10% of all Lynch syndrome-associated mutations have been attributed to alterations in MSH6[326]. Carriers of mutations in MSH6 have a 60-80% risk of colorectal cancer[327]. Lynch syndrome has an estimated prevalence in the general population ranging from 1:600 to 1:2000[325,328-329], and in the appropriate clinical context, germline testing of MSH6 is recommended.

GENE
NT5C2

ALTERATION
R367Q

POTENTIAL TREATMENT STRATEGIES

There are no therapies available to target alterations in NT5C2, although inactivation of cN-II to increase sensitivity of tumors to nucleoside analogs is of interest and has been explored in preclinical studies[330-335].

FREQUENCY & PROGNOSIS

Somatic mutations in NT5C2 are exceedingly rare in untreated patients with solid or hematologic tumors and are reported in fewer than 0.1% of cases[336]. However, NT5C2 mutations have been identified in 19-38% (n = 13-103) of T-ALL and 3-45% (n = 20-71) of B-ALL cases at chemotherapy relapse[337-341] and have been significantly associated with earlier relapse in ALL[337-338,340]. Elevated NT5C2 mRNA expression has also been associated with poorer survival in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) treated with cytarabine[342-344]. Although NT5C2 single nucleotide polymorphisms (SNPs) have been identified in patients with solid tumors treated with gemcitabine[345-346], the significance of NT5C2 alterations in the context of solid tumors is less clear (PubMed, 2017).

FINDING SUMMARY

NT5C2 encodes cytosolic 5'-nucleotidase type II (cN-II, also known as NT5B), a ubiquitous enzyme that catalyzes the dephosphorylation of nucleoside monophosphates to regulate cellular purine nucleotide pools and metabolism[347]. Dephosphorylation by cN-II also inactivates the cytotoxic metabolites of nucleoside analogs used in the treatment of cancer[348-350]. Recurrent activating mutations in NT5C2, including R238W, K359Q, R367Q, L375F, D407A, and S445F, have been identified in relapsed patients with childhood acute lymphoblastic leukemia (ALL) and are thought to drive resistance to nucleoside analog chemotherapy[337-340,351].

GENE
POLE

ALTERATION
A456P

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies that directly address POLE mutations. However, increased mutation load, such as may occur in 'ultramutated' cancers harboring deleterious mutations in POLE, has been reported to be associated with response to the anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[5,8] and nivolumab[11,352]. In particular, a patient with non-small cell lung cancer harboring a deleterious POLE mutation achieved durable clinical benefit on pembrolizumab[5]; two patients with POLE-mutated endometrial cancer responded to pembrolizumab[8] or nivolumab[9]; a patient with POLE-mutated, TMB-high, MSS colorectal cancer responded to pembrolizumab[353]; and two patients with biallelic mismatch repair deficiency (bMMRD)-associated glioblastoma harboring POLE mutations experienced clinically and radiologically significant responses to nivolumab[11]. Furthermore, POLE-mutated endometrial cancers have been shown to have higher predicted neoantigen load, increased numbers of tumor-infiltrated lymphocytes (TILs), and higher expression of PD-1 and PD-L1 in the TILs[354], which are potential biomarkers of response to anti-PD-1 immunotherapies.

FREQUENCY & PROGNOSIS

POLE alterations have been reported in 1.8% (1/56) of cases in the Uterine Carcinosarcoma TCGA dataset (cBioPortal, Jun 2017). In the context of endometrial carcinoma, POLE mutations are associated with high tumor grade[355] and correlate with better prognosis, with the most favorable prognosis seen for high-grade tumors[356-358]. Improved prognosis has also been reported for giant cell high-grade gliomas harboring POLE mutations[359].

FINDING SUMMARY

POLE encodes the catalytic subunit A of DNA polymerase epsilon, which plays roles in DNA replication and repair[360]. Deleterious mutations in POLE, mainly located within the exonuclease domain (amino acids 268–471) and reported at hot spot residues F104, D275, P286, S297, N363, D368, V411, L424, P436, R446, A456, Y458, S459, and S461, are predicted to disrupt the proofreading function of the enzyme, resulting in a high mutation rate and contributing to the development of 'ultramutated,' microsatellite-stable cancers[11,15,20-22,352,355,361-368]. Germline mutations in POLE underlie polymerase proofreading-associated polyposis (PPAP), a highly penetrant, autosomal dominant disorder characterized by the development of adenomatous polyps and an increased risk of colorectal and endometrial cancers[20-21,361-362,369].

Electronically signed by Jeff Ross, M.D. | Jeffrey Ross, M.D., Medical Director | 27 April 2018 | Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

GENE
RB1

ALTERATION
E323*

POTENTIAL TREATMENT STRATEGIES

There are no therapeutic options to target the inactivation of Rb. Preclinical studies are actively investigating possible therapies to address Rb inactivation, exploring avenues such as Aurora kinase inhibitors, BCL2 family inhibitors, and NOTCH pathway activation[370-372]. Rb loss may predict resistance to CDK4/6 inhibitors that act upstream of Rb[373-376].

FREQUENCY & PROGNOSIS

RB1 mutation has been reported in 14% (3/22) of uterine and ovarian carcinosarcoma tumors analyzed in the TCGA dataset[14]. The significance of RB1 alterations specifically in uterine carcinosarcoma has not been extensively studied (PubMed, Feb 2017).

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[377-378]. RB1 alterations that disrupt or remove the pocket domain (aa 373-771) and/or the C-terminal domain (aa 773-928), such as observed here, are predicted to be inactivating[379-385]. Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[386]. Germline mutations in RB1 account for approximately 40% of RB tumors[387] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[388-389]. In the appropriate clinical context, germline testing of RB1 is recommended.

GENE
TP53

ALTERATION
S127F, Y327*

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[390-393], therapies that reactivate mutant p53 such as APR-246[394-397], or p53 gene therapy and immunotherapeutics such as SGT-53[398-402] and ALT-801[403]. In a Phase 1 study, AZD1775 in combination with gemcitabine, cisplatin, or carboplatin elicited partial response in 10% (17/176) and stable disease in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53-wild-type[404]. 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[405]. 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[406]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% disease control rate[394]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including two confirmed and one unconfirmed partial responses and two instances of stable disease with significant tumor shrinkage[402]. 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[407]. Kevetrin has also been reported to activate p53 in preclinical studies and might be relevant in the context of mutant p53[408]. Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

FREQUENCY & PROGNOSIS

TP53 mutation has been reported to be the most common alteration present in uterine carcinosarcoma, cited in up to 75% of cases in the scientific literature, and has been found in both the carcinoma and sarcoma components[29,105,409]. Overexpression of the p53 protein has also been detected in 28-70% of uterine carcinosarcoma cases, with equal expression reported in the carcinoma and sarcoma components[29,410-413]. TP53 mutation has been correlated with decreased survival in patients with gynecological carcinosarcomas[105].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[414]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[415-417]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[418-423]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[424] to 1:20,000[423], and in the appropriate clinical context, germline testing of TP53 is recommended.

Atezolizumab

Assay findings association

Tumor Mutational Burden
TMB-High (53 Muts/Mb)

APPROVED INDICATIONS

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with advanced urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy or who progress during or following platinum-based chemotherapy and to treat patients with metastatic non-small cell lung cancer (NSCLC) and disease progression on prior treatments.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with urothelial carcinoma[2], non-small cell lung cancer[425], or melanoma[426], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-L1 therapies such as atezolizumab.

SUPPORTING DATA

Atezolizumab has been studied primarily for the treatment of non-small cell lung cancer (NSCLC)[427-428 429-430431-432] and urothelial carcinoma[433-434 2.435]. A study of atezolizumab as monotherapy for patients with advanced solid tumors reported a median progression-free survival (PFS) of 18 weeks and an overall response rate (ORR) of 21%, including confirmed responses in 26% (11/43) of melanomas, 13% (7/56) of renal cell carcinomas (RCC) and 13% (1/6) of colorectal cancers (CRCs)[432]. A Phase 1a study of atezolizumab reported an ORR of 15% (9/62), median PFS of 5.6 months, and median overall survival (OS) of 28.9 months for patients with clear cell RCC[436]. A Phase 1b study evaluated atezolizumab combined with nab-paclitaxel for patients with previously treated metastatic triple-negative breast cancer (mTNBC) and reported confirmed objective responses for 42% (10/24) of patients; no dose-limiting toxicities were observed[437]. A Phase 1b study evaluated atezolizumab in combination with the MEK inhibitor cobimetinib for advanced solid tumors and enrolled 23 patients with CRC, who were mostly (22/23) KRAS-mutant; 17% (4/23) of these patients achieved objective partial responses, with three of the responders being mismatch repair (MMR)-proficient and one of them having unknown MMR status. In addition, stable disease was observed for 22% (5/23) of patients, and no dose-limiting toxicities were encountered[438].

Avelumab

Assay findings association

Tumor Mutational Burden
TMB-High (53 Muts/Mb)

APPROVED INDICATIONS

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with metastatic Merkel cell carcinoma.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with urothelial carcinoma[2], non-small cell lung cancer[425,439], or melanoma[3], high tumor mutation burden (TMB) may predict sensitivity to immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as avelumab.

SUPPORTING DATA

The JAVELIN Phase 1b study has demonstrated clinical benefit from single-agent avelumab in a variety of solid tumor types, including non-small cell lung carcinoma (NSCLC)[440], gastric carcinoma and gastroesophageal junction (GEJ) adenocarcinoma[441], urothelial carcinoma[442], mesothelioma[443], ovarian carcinoma[444], and breast cancer[445], and from avelumab combined with axitinib in renal cell carcinoma[446]. Emerging clinical data show a positive trend toward the association of tumor cell PD-L1 expression and improved objective response rate, progression-free survival, or overall survival in NSCLC and ovarian and breast cancer[444-445 440,447]. Limited clinical data indicate activity of avelumab in adrenocortical carcinoma, metastatic castration-resistant prostate cancer, and thymic cancer[448-449 450]. Phase 3 studies are evaluating avelumab with chemoradiotherapy alone (NCT02952586) or in combination with cetuximab (NCT02999087) in patients with locally advanced head and neck squamous cell carcinoma (Mar 2017).

Durvalumab

Assay findings association

Tumor Mutational Burden
TMB-High (53 Muts/Mb)

APPROVED INDICATIONS

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with advanced urothelial carcinoma that has progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy. Durvalumab is also approved to treat patients with unresectable, Stage 3 non-small cell lung cancer that has not progressed following concurrent platinum-based chemotherapy and radiation.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with urothelial carcinoma[2], non-small cell lung cancer[425,439], or melanoma[3], high tumor mutational burden (TMB) may predict sensitivity to immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as durvalumab.

SUPPORTING DATA

Single-agent durvalumab has demonstrated efficacy in urothelial carcinoma[451-452], non-small cell lung cancer[453-454], and head and neck squamous cell carcinoma[455-456]. In patients with advanced solid tumors, durvalumab monotherapy has elicited disease control rates (DCRs) of 36-46% (7/19 to 12/26) in Phase 1/2 studies[457-458]. Durvalumab is also under investigation in combination with other agents in Phase 1/2 trials. In advanced melanoma, durvalumab in combination with trametinib and dabrafenib elicited objective response rates (ORRs) and DCRs of 76% (16/21) and 100% (21/21) in patients with BRAF-mutant tumors, and durvalumab with trametinib elicited ORRs and DCRs of 21% (3/14) and 64% (9/14) in patients whose tumors were BRAF wild-type[459]. Durvalumab in combination with the PARP inhibitor olaparib has shown activity in patients with metastatic castration-resistant prostate cancer and progression on enzalutamide and/or abiraterone[460] and in patients with BRCA-wild-type breast or gynecological cancer[461]. Responses have also been reported for patients with solid tumors treated with durvalumab in combination with the anti-PD-1 antibody MEDI0680[462], the CXCR2 antagonist AZD5069[463], or the ATR inhibitor AZD6738[464]. In patients with treatment-refractory solid tumors, concurrent durvalumab and radiotherapy achieved an ORR of 60% (6/10) for in-field evaluable lesions, including 2 complete and 4 partial responses[465].

Everolimus

Assay findings association

FBXW7
R465C

PIK3CA
M1043I, R88Q

PTEN
E7*, F341V, S179I

APPROVED INDICATIONS

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract; and, in association with tuberous sclerosis complex (TSC), renal angiomyolipoma and subependymal giant cell astrocytoma. Everolimus is also approved to treat hormone receptor-positive, HER2-negative advanced breast cancer in combination with exemestane following prior therapy with letrozole or anastrozole, as well as in combination with the multikinase inhibitor lenvatinib to treat advanced RCC following prior antiangiogenic therapy.

GENE ASSOCIATION

On the basis of extensive clinical[88-89,92] and preclinical[93] evidence in multiple tumor types, PIK3CA activation may predict sensitivity to mTOR inhibitors such as everolimus. Based on strong clinical evidence from studies of several patients with lung, renal, liver, and other cancers[55-57] and extensive preclinical evidence[53,466-467], FBXW7 loss or inactivation may predict sensitivity to mTOR inhibitors such as everolimus. Specifically, In one study of patients with different tumor types, 7/10 patients with FBXW7-mutated tumors treated with various mTOR inhibitors achieved stable disease for 2.2-6.8+ months; the patient who showed the best response carried an FBXW7 mutation as the only detectable mutation[57]. PTEN inactivation may predict benefit from mTOR inhibitors, such as everolimus, based on clinical data in various tumor types. For patients with prostate cancer, PTEN loss correlated with response to single-agent everolimus[468]. Retrospective clinical data suggest that patients with advanced breast cancer and PTEN inactivation, particularly in the context of HER2-positive disease, may benefit from everolimus combined with targeted therapy and/or chemotherapy[89,469-470].

SUPPORTING DATA

In a Phase 1 study of everolimus in combination with sorafenib, of the 22 enrolled patients with advanced solid tumors, the best response was stable disease (SD) lasting 168 days in a patient with uterine carcinosarcoma[471]. A patient with a mixed Mullerian tumor exhibited a partial response (PR) in a Phase 1 trial of a rapamycin analog, deforolimus[472]. However, a study of the mTOR inhibitor ridaforolimus as a single agent reported no clinical response in 5 patients with uterine carcinosarcoma[473]. Everolimus has been evaluated in recurrent endometrial cancer in multiple Phase 2 studies. In a Phase 2 clinical trial in recurrent endometrial cancer, 43% (12/28) of patients reported stable disease (SD) at 8 weeks and 21% (6/28) of patients achieved clinical benefit at 20 weeks upon administration of everolimus; neither PIK3CA nor PTEN mutational status was determined for patients in this trial[474]. In another Phase 2 study, everolimus was given in combination with the aromatase inhibitor letrozole, and an objective response rate in 31% (11/35) of patients with recurrent endometrial carcinoma, including 9 complete responses (CRs) and 2 PRs, was reported[475]. A Phase 2 study reported a partial response or stable disease in 35% of patients with advanced endometrial carcinoma studied; none of the PI3K-mTOR pathway proteins studied were predictive of a drug response, although KRAS mutation was suggested to predict a lack of response[476]. A study observed that 27% (6/22) of patients with HR+ breast or gynecologic malignancies and molecular alterations in the PI3K-AKT-mTOR pathway derived clinical benefit (CR, PR, or SD for at least 6 months) from everolimus combined with anastrozole[469]. A Phase 1b trial of a combination of trametinib and the mTOR inhibitor everolimus in patients with solid tumors reported frequent adverse events, and the study was unable to identify a recommended Phase 2 dose and schedule for the combination[477].

Nivolumab

Assay findings association

Tumor Mutational Burden
TMB-High (53 Muts/Mb)

APPROVED INDICATIONS

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby reducing inhibition of the antitumor immune response. It is FDA approved to treat unresectable or metastatic melanoma as both a single agent and in combination with the immunotherapy ipilimumab. Nivolumab is also approved to treat metastatic non-small cell lung cancer (NSCLC) following disease progression on prior treatments, advanced renal cell carcinoma after prior antiangiogenic therapy, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) following disease progression on or after platinum-based therapy, advanced urothelial carcinoma that has progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy, hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib, and classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. Furthermore, nivolumab is approved to treat patients 12 years and older with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with non-small cell lung cancer[5,425], colorectal cancer[6], or melanoma[426] and case reports in endometrial cancer[8-9] and glioblastoma[11], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-1 therapies such as nivolumab.

SUPPORTING DATA

A case study reported partial responses to nivolumab in 2 patients with endometrial carcinoma harboring high tumor mutation burden; response was ongoing at 7-9 months[9].

Pembrolizumab

Assay findings association

Tumor Mutational Burden
TMB-High (53 Muts/Mb)

APPROVED INDICATIONS

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved as second-line treatment for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors or with MSI-H or dMMR colorectal cancer that has progressed on a fluoropyrimidine, oxaliplatin, and irinotecan. Pembrolizumab is also approved in unresectable or metastatic melanoma; recurrent or metastatic head and neck squamous cell carcinoma that has progressed on or after platinum chemotherapy; adult or pediatric classical Hodgkin lymphoma that is refractory or following relapse after three or more prior lines of therapy; advanced urothelial carcinoma that is not eligible for cisplatin-containing chemotherapy, has progressed on or after platinum chemotherapy, or has progressed within 12 months of neoadjuvant or adjuvant platinum chemotherapy; and PD-L1-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma that has progressed on two or more lines of therapy. Pembrolizumab is approved in PD-L1-positive metastatic non-small cell lung cancer (NSCLC) following progression on prior therapy, as first-line treatment for metastatic NSCLC with high PD-L1 expression and without EGFR or ALK genomic alterations, and as first-line treatment in combination with pemetrexed and carboplatin for metastatic nonsquamous NSCLC.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with non-small cell lung cancer[5,425], colorectal cancer[6], or melanoma[426] and case reports in endometrial cancer[8-9] and glioblastoma[11], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-1 therapies such as pembrolizumab.

SUPPORTING DATA

Pembrolizumab achieved clinical benefit for 25% [3/24 partial responses (PRs) and 3/24 stable disease (SD)] of patients with previously treated advanced endometrial carcinoma and PD-L1 expression in at least 1% of cells; the 6-month progression-free survival and overall survival (OS) rates were 19% and 69%, respectively[478]. Preliminary results from a Phase 2 study of pembrolizumab for patients with MMR-deficient recurrent endometrial cancer reported 1 complete response (CR), 4 PRs, and 3 SDs; the patient who achieved a CR remained disease-free for 17 months[479]. A patient with PD-L1-positive POLE-mutant endometrial adenocarcinoma and high tumor mutational burden experienced a PR to pembrolizumab for more than 14 months[8]. In a Phase 1/2 study of pembrolizumab and epacadostat in multiple solid tumor types, a PR was reported for 1 of 2 patients with endometrial adenocarcinoma[480]. A Phase 2 basket study of pembrolizumab for patients with mismatch repair-deficient non-colorectal advanced solid tumors (n=29), including 9 endometrial cancer cases, reported objective responses for 48% (14/29), SD for 24% (7/29), and 1-year OS for 79% of patients[459].

Temsirolimus

Assay findings association

FBXW7
R465C

PIK3CA
M1043I, R88Q

PTEN
E7*, F341V, S179I

APPROVED INDICATIONS

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma.

GENE ASSOCIATION

On the basis of extensive clinical[90-91,481] and preclinical[93] evidence, PIK3CA activation may predict sensitivity to mTOR inhibitors such as temsirolimus. In two studies of temsirolimus-containing treatment regimens in a variety of cancer types, response rates of 4/16 (25%)[90] and 7/23 (30%)[481] were reported in patients with PIK3CA-mutant tumors. Based on strong clinical evidence from studies of several patients with lung, liver, and other cancers[55,57] and extensive preclinical evidence[53,466-467], FBXW7 loss or inactivation may predict sensitivity to mTOR inhibitors such as temsirolimus. PTEN inactivation may predict benefit from mTOR inhibitors, such as temsirolimus, based on clinical data in various tumor types. Out of 10 patients with metaplastic breast cancer and PTEN alterations, 2 cases responded to temsirolimus or everolimus plus doxorubicin and bevacizumab[91,482]. Temsirolimus achieved stable disease for 6 of 7 patients with PTEN-deficient cervical carcinoma[483]. Clinical studies in renal cell carcinoma[484-485], glioblastoma[486-487], or endometrial cancer[488-491] did not observe a correlation of PTEN deficiency with response to temsirolimus, although several patients with those tumor types and PTEN loss have benefited from mTOR inhibitors.

SUPPORTING DATA

In a Phase 1 trial of 74 patients with breast and gynecological malignancies examining the combination of temsirolimus, liposomal doxorubicin, and bevacizumab, researchers reported that 37.9% of patients experienced either a complete response (1.4%), partial response (18.9%) or stable disease (17.6%)[492]. A Phase 2 clinical trial of temsirolimus in recurrent or metastatic endometrial cancer reported partial response in 4/29 (14%) chemotherapy-naïve patients and 1/25 (4%) chemotherapy-treated patients, with stable disease reported in 20/29 (69%) chemotherapy-naïve patients and 12/25 (48%) chemotherapy-treated patients; however, response in this study was found to be independent of molecular markers of PI3K-AKT-mTOR pathway activation[488]. A study of the mTOR inhibitor ridaforolimus as a single agent reported no clinical response in 5 patients with uterine carcinosarcoma[473]. Furthermore, a study of the combination of temsirolimus and topotecan was investigated in endometrial cancers, including 3 patients with carcinosarcoma, with 9/15 patients experiencing stable disease; however, this regimen was not well tolerated in patients who had previously received radiation therapy[493].

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.

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

BIOMARKER

Tumor Mutational Burden

CATEGORY

TMB-High (53 Muts/Mb)

RATIONALE

High tumor mutational burden may predict response to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors. 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 "PD-L1", "B7-H1", "PD-1", "pembrolizumab", "nivolumab", "atezolizumab", "MPDL3280A", "durvalumab", "MEDI4736", "avelumab", "MSB0010718C", "BMS-936559", "CT-011", "uterine carcinosarcoma", "solid tumor", and/or "advanced cancer".

NCT02834013

PHASE 2

DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors

TARGETS
CTLA-4, PD-1

LOCATIONS: Nevada, Florida, Kentucky, North Carolina, Kansas, Idaho, Wisconsin, Washington, Colorado, Iowa, Mississippi, Alaska, Missouri, Delaware, North Dakota, Montana, Ohio, Tennessee, South Dakota, District of Columbia, New York, Louisiana, New Hampshire, Oklahoma, Wyoming, Hawaii, Massachusetts, Utah, Maryland, South Carolina, Vermont, California, Oregon, Michigan, Indiana, Alabama, West Virginia, Nebraska, Illinois, Minnesota, Georgia, Connecticut, Texas, Pennsylvania, New Mexico, Arkansas

NCT02091141

PHASE 2

My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

TARGETS
EGFR, PD-L1, ALK, BRAF, RET, ERBB2, ERBB3, MEK, SMO

LOCATIONS: Ohio, Colorado, Virginia, Florida, Minnesota, Oregon, North Carolina, Missouri, California, Arkansas, Maryland, Tennessee, Wisconsin, Georgia, Texas, North Dakota, Illinois, South Dakota, New York, Oklahoma, Arizona, Washington, Pennsylvania

NCT02118337

PHASE 1 / PHASE 2

A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination With MEDI4736 and MEDI0680 Monotherapy in Subjects With Select Advanced Malignancies

TARGETS
PD-L1, PD-1

LOCATIONS: California, New Jersey, Oregon, Kansas, Kentucky, Florida, New York, South Carolina, New Hampshire, West Virginia, Ohio, Minnesota, Oklahoma, Washington, Pennsylvania

NCT02693535

PHASE 2

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
ABL, CDK4, PARP, EGFR, DDR2, VEGFRs, PDGFRs, ROS1, CSF1R, ERBB2, PD-1, ERBB3, MEK, RAF1, KIT, SMO, AXL, TRKC, mTOR, TRKA, MET, ALK, BRAF, RET, SRC, FLT3, CDK6

LOCATIONS: North Dakota, Pennsylvania, Washington, Illinois, Georgia, Arizona, Utah, North Carolina, Oklahoma, South Dakota, Michigan, Oregon, Nebraska

CLINICAL TRIALS

NCT02253992	PHASE 1/PHASE 2
A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Tolerability of Urelumab Administered in Combination With Nivolumab in Advanced/Metastatic Solid Tumors and B-cell Non-Hodgkins Lymphoma	TARGETS PD-1, 4-1BB

LOCATIONS: California, Florida, Illinois, Maryland, Massachusetts, New York, Pennsylvania, Texas, Besancon (France), Essen (Germany), Marseille (France), Rennes Cedex 9 (France), Villejuif (France)

NCT01968109	PHASE 1/PHASE 2
A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination With Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors	TARGETS LAG-3, PD-1

LOCATIONS: Illinois, Maryland, Massachusetts, Michigan, Missouri, New York, Oregon, Pennsylvania, Texas, Washington, Amsterdam (Netherlands), Barcelona (Spain), Copenhagen (Denmark), Essen (Germany), Greater London (United Kingdom), Heilbronn (Germany), Helsinki (Finland), Herlev (Denmark), Lausanne (Switzerland), London (United Kingdom), Malaga (Spain), Manchester (United Kingdom), Marseille Cedex 5 (France), Milano (Italy), Nantes Cedex 01 (France), Napoli (Italy), New South Wales (Australia), Oslo (Norway), Padova (Italy), Pamplona (Spain), Pierre Benite Cedex (France), Queensland (Australia), Tokyo (Japan), Toulouse Cedex 9 (France), Vlllejuif (France), Western Australia (Australia), Wien (Austria), Wuerzburg (Germany), Zurich (Switzerland)

NCT02546531	PHASE 1
Phase I Study of Defactinib Combined With Pembrolizumab and Gemcitabine in Patients With Advanced Cancer	TARGETS FAK, PD-1

LOCATIONS: Missouri

NCT02646748	PHASE 1
A Platform Study Exploring the Safety, Tolerability, Effect on the Tumor Microenvironment, and Efficacy of Pembrolizumab + INCB Combinations in Advanced Solid Tumors	TARGETS JAK1, PI3K-delta, PD-1

LOCATIONS: Florida, Massachusetts, District of Columbia, New York, North Carolina, Pennsylvania, California

NCT02453620	PHASE 1
A Phase 1 Study Evaluating Safety, Tolerability, and Preliminary Antitumor Activity of Entinostat and Nivolumab With or Without Ipilimumab in Advanced Solid Tumors	TARGETS HDAC, CTLA-4, PD-1

LOCATIONS: Maryland, Connecticut, Pennsylvania, California

NCT02484404	PHASE 1 / PHASE 2
Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers	TARGETS PARP, PD-L1, VEGFRs

LOCATIONS: Maryland

CLINICAL TRIALS

GENE
FBXW7

ALTERATION
R465C

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation. Therefore, mTOR inhibitors may be of use in a tumor with loss or mutation of FBXW7. 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 "mTOR", "everolimus", "temsirolimus", "uterine carcinosarcoma", "solid tumor", and/or "advanced cancer".

NCT01529593 — **PHASE 1**

Phase I Study of Temsirolimus in Combination With Metformin in Patients With Advanced Cancers

TARGETS
AMPK, mTOR

LOCATIONS: Texas

NCT01582191 — **PHASE 1**

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
EGFR, RET, SRC, VEGFRs, mTOR

LOCATIONS: Texas

NCT01552434 — **PHASE 1**

A Phase I Trial of Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
HDAC, EGFR, VEGFA, mTOR

LOCATIONS: Texas

NCT02321501 — **PHASE 1**

A Phase I/Ib Dose Escalation and Biomarker Study of Ceritinib (LDK378) in Combination With Everolimus in Patients With Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ALK, ROS1, mTOR

LOCATIONS: Texas

NCT02159989 — **PHASE 1**

Phase I Study of MLN0128 (TAK-228) (NSC# 768435) in Combination With Ziv-Aflibercept (NSC# 724770) in Patients With Advanced Cancers

TARGETS
VEGFA, VEGFB, PIGF, mTORC1, mTORC2

LOCATIONS: Texas

NCT03065062 — **PHASE 1**

Phase I Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
CDK4, mTORC1, PI3K-gamma, mTORC2, PI3K-alpha, CDK6

LOCATIONS: Massachusetts

NCT02142803 — **PHASE 1**

A Phase 1 Study of MLN0128 and Bevacizumab in Patients With Recurrent Glioblastoma and Other Solid Tumors

TARGETS
VEGFA, mTORC1, mTORC2

LOCATIONS: Massachusetts

CLINICAL TRIALS

NCT02719691	PHASE 1
A Phase Ib Study of the Combination of MLN0128 (Dual TORC1/2 Inhibitor) and MLN8237 (Aurora A Inhibitor, Alisertib) in Patients With Advanced Solid Tumors With an Expansion Cohort in Metastatic Triple-negative Breast Cancer (TNBC)	TARGETS Aurora kinase A, mTORC1, mTORC2
LOCATIONS: Colorado	

NCT02583542	PHASE 1 / PHASE 2
A Phase Ib/IIa Study of AZD2014 in Combination With Selumetinib in Patients With Advanced Cancers	TARGETS mTORC1, MEK, mTORC2
LOCATIONS: London (United Kingdom)	

NCT02029001	PHASE 2
A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors	TARGETS BCR-ABL, CSF1R, DDR1, KIT, PDGFRs, mTOR, BRAF, CRAF, FLT3, RAF, RET, VEGFRs, EGFR, ERBB2, c-FMs, FGFR1, FGFR2, FGFR3, ITK, LCK
LOCATIONS: Bordeaux (France), Lyon (France), Marseille (France), Paris (France), Pierre-Bénite (France), Toulouse (France)	

CLINICAL TRIALS

GENE
PIK3CA

ALTERATION
M1043I, R88Q

RATIONALE
PIK3CA activating mutations or amplification may lead to activation of the PI3K-AKT-mTOR pathway, and may therefore predict sensitivity to inhibitors of PI3K, AKT, and/or mTOR. 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 "PI3K", "mTOR", "AKT", "everolimus", "temsirolimus", "uterine carcinosarcoma", "solid tumor", and/or "advanced cancer".

NCT02576444 — **PHASE 2**

A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid Tumors

TARGETS
AKTs, PARP, WEE1, mTORC1, mTORC2

LOCATIONS: Connecticut, Massachusetts, Tennessee

NCT01226316 — **PHASE 1**

A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD5363 Under Adaptable Dosing Schedules in Patients With Advanced Solid Malignancies.

TARGETS
AKTs

LOCATIONS: Vancouver (Canada), Chuo-ku (Japan), Villejuif (France), Pierre Benite Cedex (France), Napoli (Italy), Amsterdam (Netherlands), København Ø (Denmark), Tennessee, Barcelona (Spain), Koto-ku (Japan), Singapore (Singapore), Paris Cedex 5 (France), Milano (Italy), Kashiwa-shi (Japan), California, Prato (Italy), Sapporo-shi (Japan), Toronto (Canada), Colorado, Montreal (Canada), Texas, Valencia (Spain), Connecticut, South Carolina, New York, Oklahoma, Madrid (Spain), Edmonton (Canada), Pennsylvania

NCT02476955 — **PHASE 1**

An Open-label Phase 1b Study of ARQ 092 in Combination With Carboplatin Plus Paclitaxel, in Combination With Paclitaxel, or in Combination With Anastrozole in Subjects With Selected Solid Tumors

TARGETS
AKTs, Aromatase

LOCATIONS: New York, Michigan, Texas

NCT02253420 — **PHASE 1**

An Open-label Non-randomized, Phase 1 Study to Evaluate the Effect of (a) Itraconazole or Rifampin on the Pharmacokinetics of a Single Intravenous Dose of Copanlisib and (b) Copanlisib on Cardiovascular Safety in Subjects With Advanced Solid Tumors

TARGETS
PI3K

LOCATIONS: Hamilton (Canada), Toronto (Canada), Edmonton (Canada)

NCT02307240 — **PHASE 1**

Phase I Open Label, Multi-center Study to Assess the Safety, Tolerability and Pharmacokinetics of Orally Administered CUDC-907, an HDAC and PI3K Inhibitor, in Subjects With Advanced/Relapsed Solid Tumors

TARGETS
HDAC, PI3K

LOCATIONS: California, Texas, Florida, Massachusetts

NCT02321501 — **PHASE 1**

A Phase I/Ib Dose Escalation and Biomarker Study of Ceritinib (LDK378) in Combination With Everolimus in Patients With Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ALK, ROS1, mTOR

LOCATIONS: Texas

CLINICAL TRIALS

NCT01582191	PHASE 1
A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer	TARGETS EGFR, RET, SRC, VEGFRs, mTOR
LOCATIONS: Texas	

NCT01552434	PHASE 1
A Phase I Trial of Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications	TARGETS HDAC, EGFR, VEGFA, mTOR
LOCATIONS: Texas	

NCT01529593	PHASE 1
Phase I Study of Temsirolimus in Combination With Metformin in Patients With Advanced Cancers	TARGETS AMPK, mTOR
LOCATIONS: Texas	

NCT02761694	PHASE 1
A Phase 1 Dose Escalation Study of ARQ 751 in Adult Subjects With Advanced Solid Tumors With AKT1, 2, 3 Genetic Alterations, Activating PI3K Mutations or PTEN-null	TARGETS AKTs
LOCATIONS: Texas	

GENE
PTEN

ALTERATION
E7*, F341V, S179I

RATIONALE
PTEN loss or inactivating mutation may predict sensitivity to PI3K-AKT-mTOR pathway inhibitors or PARP inhibitors. 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 "PTEN", "PI3K", "AKT", "mTOR", "everolimus", "temsirolimus", "PARP", "olaparib", "rucaparib", "BMN 673", "ABT-888", "veliparib", "E7449", "niraparib", "uterine carcinosarcoma", "solid tumor", and/or "advanced cancer".

NCT02576444 — **PHASE 2**

A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid Tumors

TARGETS
AKTs, PARP, WEE1, mTORC1, mTORC2

LOCATIONS: Connecticut, Massachusetts, Tennessee

NCT02921919 — **PHASE 2**

A Single-arm, Open-label, Multicenter, Extended Treatment, Safety Study In Patients Treated With Talazoparib

TARGETS
PARP

LOCATIONS: New Jersey, Michigan, Hamilton (Canada), Moscow (Russian Federation), Florida, Indiana, Edmonton (Canada), Sutton (United Kingdom), Chisinau (Moldova, Republic of), Saint-Petersburg (Russian Federation), Montreal (Canada), California, Texas, Budapest (Hungary)

NCT01226316 — **PHASE 1**

A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD5363 Under Adaptable Dosing Schedules in Patients With Advanced Solid Malignancies.

TARGETS
AKTs

LOCATIONS: Vancouver (Canada), Chuo-ku (Japan), Villejuif (France), Pierre Benite Cedex (France), Napoli (Italy), Amsterdam (Netherlands), København Ø (Denmark), Tennessee, Barcelona (Spain), Koto-ku (Japan), Singapore (Singapore), Paris Cedex 5 (France), Milano (Italy), Kashiwa-shi (Japan), California, Prato (Italy), Sapporo-shi (Japan), Toronto (Canada), Colorado, Montreal (Canada), Texas, Valencia (Spain), Connecticut, South Carolina, New York, Oklahoma, Madrid (Spain), Edmonton (Canada), Pennsylvania

NCT02511795 — **PHASE 1**

A Phase Ib Study of AZD1775 and Olaparib in Patients With Refractory Solid Tumours

TARGETS
PARP, WEE1

LOCATIONS: Colorado, Florida, Toronto (Canada), New York, Texas, Tennessee

NCT01012817 — **PHASE 1 / PHASE 2**

A Phase I/II Trial of ABT-888, an Inhibitor of Poly(ADP-Ribose) Polymerase (PARP), and Topotecan (TPT) in Patients With Solid Tumors (Phase I) and Relapsed Ovarian Cancer or Primary Peritoneal Cancer (Phase II) After Prior Platinum Containing First-Line Chemotherapy

TARGETS
PARP, TOP1

LOCATIONS: Pennsylvania, Minnesota, Illinois, California, Kansas, Arizona

NCT02476955 — **PHASE 1**

An Open-label Phase 1b Study of ARQ 092 in Combination With Carboplatin Plus Paclitaxel, in Combination With Paclitaxel, or in Combination With Anastrozole in Subjects With Selected Solid Tumors

TARGETS
AKTs, Aromatase

LOCATIONS: New York, Michigan, Texas

CLINICAL TRIALS

NCT01366144 — **PHASE 1**

An Early Phase 1 Study of ABT-888 in Combination With Carboplatin and Paclitaxel in Patients With Hepatic or Renal Dysfunction and Solid Tumors

TARGETS
PARP

LOCATIONS: Maryland, New Jersey, Pennsylvania, New York, Texas, California, Wisconsin, Massachusetts, Michigan

NCT01884285 — **PHASE 1**

A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Anti-tumour Activity of AZD8186 in Patients With Advanced Castration-resistant Prostate Cancer (CRPC), Squamous Non-Small Cell Lung Cancer (sqNSCLC), Triple Negative Breast Cancer (TNBC) and Patients With Known PTEN-deficient/Mutated or PIK3CB Mutated/ Amplified Advanced Solid Malignancies as Monotherapy and in Combination With Abiraterone Acetate or AZD2014

TARGETS
mTORC1, PI3K-beta, mTORC2, CYP17

LOCATIONS: Barcelona (Spain), Toronto (Canada), New York, Wisconsin, Massachusetts, Michigan, London (United Kingdom), Washington, Manchester (United Kingdom), Sutton (United Kingdom)

NCT02317874 — **PHASE 1**

A Phase 1 Study of BMN 673 in Combination With Carboplatin and Paclitaxel in Patients With Advanced Solid Tumors

TARGETS
PARP

LOCATIONS: New Jersey, Wisconsin

NCT02484404 — **PHASE 1 / PHASE 2**

Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers

TARGETS
PARP, PD-L1, VEGFRs

LOCATIONS: Maryland

NCT01582191 — **PHASE 1**

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
EGFR, RET, SRC, VEGFRs, mTOR

LOCATIONS: Texas

NCT02307240 — **PHASE 1**

Phase I Open Label, Multi-center Study to Assess the Safety, Tolerability and Pharmacokinetics of Orally Administered CUDC-907, an HDAC and PI3K Inhibitor, in Subjects With Advanced/Relapsed Solid Tumors

TARGETS
HDAC, PI3K

LOCATIONS: California, Texas, Florida, Massachusetts

NCT02761694 — **PHASE 1**

A Phase 1 Dose Escalation Study of ARQ 751 in Adult Subjects With Advanced Solid Tumors With AKT1, 2, 3 Genetic Alterations, Activating PI3K Mutations or PTEN-null

TARGETS
AKTs

LOCATIONS: Texas

Electronically signed by Jeff Ross, M.D. | Jeffrey Ross, M.D., Medical Director | 27 April 2018 | Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

CLINICAL TRIALS

NCT02719691	PHASE 1
A Phase Ib Study of the Combination of MLN0128 (Dual TORC1/2 Inhibitor) and MLN8237 (Aurora A Inhibitor, Alisertib) in Patients With Advanced Solid Tumors With an Expansion Cohort in Metastatic Triple-negative Breast Cancer (TNBC)	**TARGETS** Aurora kinase A, mTORC1, mTORC2

LOCATIONS: Colorado

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.

ALOX12B I239M	***AR*** E707* and S230L	***ASXL1*** V891I	***ATM*** S2495A and S2812Y
ATRX S566Y	***AXL*** R71W	***CARD11*** F643L	***CD79A*** R168Q
CDK12 K853N	***CHEK1*** K145R	***CREBBP*** F22L	***CSF3R*** I262T
EPHA3 D356Y	***ESR1*** H6Y	***GNAS*** E676K	***JAK3*** K390N
JUN T2P	***KDM6A*** R393Q and R949C	***KDR*** D623N	***MTOR*** M2089I
NF1 L2639I	***PAX5*** S213L	***PIK3C2G*** E16K and E800A	***PIK3CA*** R357*
PPARG D490G	***PRDM1*** K241N	***PRKCI*** R523Q	***PTCH1*** R530I
PTEN L100R	***PTPRO*** N1019H	***RAD51C*** D109Y	***SDHA*** R261H
STAG2 D153N	***STAT3*** E50* and R417I	***TET2*** S153Y	***TSC2*** F1510del
WHSC1 R602W	***WHSC1L1*** R898C		

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) 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. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

INDICATION	GENOMIC FINDINGS	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), 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)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E or 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)
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	Rubraca® (Rucaparib)

TABLE 1

The median exon coverage for this sample is 945x

TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 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 microsatellite instability (MS) and tumor mutational burden (TMB) will be reported.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/f1cdx

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. Genomic findings other than those listed in Table 1 of the intended use are not prescriptive or conclusive for labeled use of any specific therapeutic product.
4. A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
5. Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*.
6. Clinical performance of Tagrisso® (osimertinib) in patients with an *EGFR* exon 20 T790M mutation detected with an allele fraction <5% is ongoing and has not been established.
7. Concordance with other validated methods for CNA (with the exception of *ERBB2*) and gene rearrangement (with the exception of *ALK*) detection has not been demonstrated and will be provided in the post-market setting. Confirmatory testing using a clinically validated assay should be performed for all CNAs and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use, but used for clinical decision making.
8. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. Refer to the Summary of Safety of Effectiveness Data (SSED) for additional details on methodology. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established.
9. TMB by F1CDx is defined based on counting the total number of all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
10. 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.
11. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.

FoundationOne CDx™ 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 324 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	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*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	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*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*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*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*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*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*	*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*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*	*PARK2*
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*	*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*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*
TSC2	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WHSC1L1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC IS A NCRNA
**THE PROMOTER REGION OF TERT INTERROGATED

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite Status (MS)
Tumor Mutational Burden (TMB)

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.

PROFESSIONAL SERVICES FINDINGS

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.

RANKING OF ALTERATIONS AND DRUGS

Biomarker Findings
Appear at the top of the report, but are not ranked higher than Genomic Findings.

Genomic Findings
Therapies with Clinical Benefit In Patient's Tumor Type → Therapies with Clinical Benefit in Other Tumor Type → Clinical Trial Options → No Known Options (if multiple findings exist within any of these categories, the results are listed alphabetically by gene name).

Therapies
Sensitizing therapies → Resistant therapies (if multiple therapies exist within any of these categories, they are listed in no particular order).

Clinical Trials
Pediatric trial qualification → Geographical Proximity → Later trial phase.

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

Foundation Medicine makes no promises or guarantees that a particular drug will be effective in the treatment of disease of 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 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 with the 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.

TUMOR MUTATIONAL BURDEN

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations occurring in sequenced genes on the FoundationOne CDx test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne CDx samples and may be reported in Professional Services as "TMB-High", "TMB-Intermediate", "TMB-Low", or "Cannot Be Determined". TMB results, which are rounded to the nearest integer, are determined as follows: TMB-High corresponds to greater than or equal to 20 mutations per megabase (muts/Mb); TMB-Intermediate corresponds to 6-19 muts/Mb; TMB-Low corresponds to fewer than or equal to 5 muts/Mb. Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

Genomic Findings with Evidence of Clinical Significance
Genomic findings listed at Level 2 are associated with clinical significance. Clinical significance may be indicated by evidence of therapeutic sensitivity or resistance and/or diagnostic, prognostic or other clinically relevant implications. Included in this category will be findings associated with clinical validity as supported by professional guidelines and/or peer-reviewed publications.

Genomic Findings with Potential Clinical Significance
Genomic findings listed at Level 3 are cancer-related mutations and biomarkers with potential clinical significance. These include findings in genes known to be associated with cancer and are supported by evidence from publicly available databases, and/or peer-reviewed publications.

A Fluid Approach to Reporting Levels
As additional information becomes available, as recognized by the clinical community (professional guidelines and/or peer-reviewed publications), findings may move between Levels 2 and 3 in accordance with the above descriptions.

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

APPENDIX References Associated with Professional Services Content

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