FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Skin squamous cell carcinoma (SCC)

REPORT DATE
22 Jan 2021

COUNTRY CODE
PE

ORDERED TEST #
ORD-0995393-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Skin squamous cell carcinoma (SCC)

DATE OF BIRTH 28 February 1961
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Skin
SPECIMEN ID Q42005
SPECIMEN TYPE Block
DATE OF COLLECTION 18 December 2020
SPECIMEN RECEIVED 14 January 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

EGFR amplification
PTEN loss exons 3-6
KEL V36M
NOTCH1 C815fs*60
ROS1 amplification
TP53 H179Q

8 Therapies with Clinical Benefit
0 Therapies with Lack of Response
20 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
EGFR - amplification	none	Cetuximab 2A
		Afatinib
		Dacomitinib
		Erlotinib
		Gefitinib
		Panitumumab
10 Trials *see p. 12*		
PTEN - loss exons 3-6	none	Everolimus
		Temsirolimus
10 Trials *see p. 14*		

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

Electronically signed by Chelsea Marcus, M.D. | 22 January 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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
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NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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

FREQUENCY & PROGNOSIS

Microsatellite instability has been reported to be uncommon in sporadic cutaneous squamous cell carcinoma (SCC)[6-8], with one study reporting low-level MSI in 4.5% (1/22) and high-level MSI in 0% (0/22) of samples[6]. The prognostic significance of MSI in cutaneous SCC has not been extensively studied (PubMed, Jan 2021).

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[9]. 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[9-11]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[12-14]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[9,11,13-14].

BIOMARKER

Tumor Mutational Burden

RESULT
4 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[15-17], anti-PD-1 therapies[15-18], and combination nivolumab and ipilimumab[19-23]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[15-18,24]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[15]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[25] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[16]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[18,24]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Cutaneous squamous cell carcinoma (SCC) has been reported to harbor a high mutational burden compared with most other tumor types, with small studies reporting mean TMBs of 26 mutations per megabase (mut/Mb) in 8 samples[26], 50 mut/Mb in 20 samples[27], and 61 mut/Mb in 39 samples[28]. In the majority of cutaneous SCC cases, the high mutational burden has been attributed to UV exposure rather than defective DNA mismatch repair or polymerase activity[27-28], although one study reported a small number of cutaneous SCC cases (4/39) harboring a mutation signature similar to that of human papillomavirus (HPV)-positive head and neck SCC (HNSCC)[28]. In cutaneous SCC, TMB correlated with histological subtype (p = 0.02), with a higher TMB identified in tumors classified as acantholytic, but did not correlate with other clinicopathologic features[28].

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[29-30] and cigarette smoke in lung cancer[31-32], treatment with temozolomide-based chemotherapy in glioma[33-34], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[35-39], and microsatellite instability (MSI)[35,38-39]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[16-17,24].

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GENE
EGFR

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

EGFR amplification or expression may be associated with benefit from anti-EGFR antibodies, such as cetuximab[40-43], panitumumab[41], or necitumumab[44], or EGFR TKIs that target wild-type EGFR[45-49]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin[50-51] that has also shown benefit in patients with CRC and melanoma[52-53]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy[54-57]. Preclinical studies have reported that EGFR-mutant cells[54-56], including cells with exon 20 insertions[58], are sensitive to HSP90 inhibitors. Consistent with preclinical data demonstrating that the EGFR inhibitor AZD3759 is capable of penetrating the blood-brain barrier and reducing the volume of brain and leptomeningeal metastases, preliminary results from a Phase 1 trial evaluating single-agent AZD3759 reported a reduction in the volume of brain metastases in 40.0% (8/20) of patients with previously treated NSCLC harboring either EGFR L858R or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[59-60]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54.3% (69/127) for all evaluable patients and 44.4% (8/18, intracranial) for patients with brain metastases[61]. The reovirus Reolysin targets cells with activated RAS signaling[62-64] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[65-73].

FREQUENCY & PROGNOSIS

EGFR mutation or protein overexpression have been reported in 77% and 78% of cutaneous squamous cell carcinoma (SCC) samples in one study, respectively[74]. Another study of 19 cutaneous SCCs found EGFR amplification to be rare in the samples examined, although increased EGFR gene copy number was reported in 73.7% (14/19) of cases[75]. Increased EGFR activity has also been reported in cutaneous SCC in one study[76]. Published data investigating the prognostic implications of EGFR alterations in cutaneous SCC are limited (PubMed, Jan 2021). One study reported EGFR protein overexpression to be associated with increased risk of lymph node metastasis (odds ratio [OR]=7.117, p=0.004) and disease progression (OR=4.858, p=0.024) in patients with cutaneous SCC[77].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[78]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[79-81].

GENE
PTEN

ALTERATION
loss exons 3-6

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[82-86] such as the mTOR inhibitors temsirolimus and everolimus or the PI3K inhibitor copanlisib. Preclinical studies suggest that PTEN-deficient cancers, in the absence of other oncogenic mutations, depend primarily on the beta isoform of PI3K (PI3K-beta)[87-89], and PI3K-beta-selective inhibitors are in clinical trials for PTEN-deficient tumors. However, the NCI-MATCH Phase 2 study observed limited activity of the PI3K-betaselective inhibitor GSK2636771 as monotherapy in PTEN-deficient cancers, with a median PFS of 1.8 months. The best outcomes were 1 PR (1/22, prostate cancer), SD (7/22) for patients with PTEN deletion/mutation, and SD (9/34) for patients with PTEN protein loss[90]. Clinical data in breast[91-92] and prostate cancer[93-94] suggest that PTEN alterations may predict sensitivity to pan-AKT inhibitors such as ipatasertib or capivasertib. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[95-99], and clinical benefit has been observed for patients with PTEN-altered breast cancer[100], ovarian cancer[101], endometrial cancer[99], and other tumor types[102] treated with PARP inhibitors. However, several studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[98,103-104]. Limited clinical evidence in glioblastoma[105], leiomyosarcoma[106], NSCLC[107], and melanoma[108] suggests that PTEN alterations may predict a lack of response to anti-PD-1 therapy. In an analysis of 39 patients with metastatic melanoma treated with pembrolizumab or nivolumab, patients with PTEN-expressing tumors achieved significantly greater reduction of tumor size than those with reduction or loss of PTEN expression[108]. In a retrospective analysis of 66 patients with glioblastoma, tumors from nivolumab or pembrolizumab non-responders were significantly enriched for PTEN mutations[105]. In a patient with uterine leiomyosarcoma treated with pembrolizumab monotherapy, a treatment-resistant tumor arose that harbored PTEN loss[106]. A patient with NSCLC whose tumor harbored a PTEN alteration exhibited a lack of response to nivolumab and pembrolizumab[107].

FREQUENCY & PROGNOSIS
In a study of cutaneous squamous cell carcinoma (SCC), PTEN mutation was observed in 7% (2/29) of sequenced tumors[109]. Decreased PTEN levels have been observed in cutaneous SCCs[110]. Published data investigating the prognostic implications of PTEN alterations in cutaneous SCC are limited (PubMed, Oct 2020).

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[84]. Alterations such as seen here may disrupt PTEN function or expression[111-151]. PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[152-153]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[152,154]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[152]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
KEL

ALTERATION
V36M

TRANSCRIPT ID
NM_000420

CODING SEQUENCE EFFECT
106G>A

VARIANT ALLELE FREQUENCY (% VAF)
48.1%

POTENTIAL TREATMENT STRATEGIES
There are no therapies available to target genomic alterations in KEL.

FREQUENCY & PROGNOSIS
KEL mutations have been reported in tumors of the skin, lung, endometrium, stomach, large intestine, soft tissue, and liver at rates of 1.9-12.6%; up to 1.2% of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic lymphocytic leukaemia-small lymphocytic lymphoma (CLL/SLL) samples; and in 9.1% (4/44) of Mycosis fungoides-Sezary syndrome samples (COSMIC, 2021)[155]. However, the mechanism by which KEL mutations contribute to tumor formation is not known.

FINDING SUMMARY
KEL encodes a transmembrane glycoprotein with similarities to zinc-dependent metalloproteases; this glycoprotein is highly polymorphic and forms the Kell blood group antigen[156].

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Foundation Medicine, Inc. | 1.888.988.3639

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GENE
NOTCH1

ALTERATION
C815fs*60

TRANSCRIPT ID
NM_017617

CODING SEQUENCE EFFECT
2442_2445delGTGC

VARIANT ALLELE FREQUENCY (% VAF)
54.9%

POTENTIAL TREATMENT STRATEGIES

NOTCH1 inhibitors and gamma-secretase inhibitors (GSIs) may be potential therapeutic approaches in the case of NOTCH1 activating mutations[157-164]. Complete responses to the GSI BMS-906024 (AL101) were achieved in a patient with T-cell acute lymphoblastic leukemia (T-ALL) harboring a NOTCH1 HD domain mutation[165] and in a patient with gastroesophageal junction adenocarcinoma harboring multiple NOTCH1 mutations, as well as a partial response in a patient with adenoid cystic carcinoma harboring a single NOTCH1 mutation[166]. BMS-906024 has been shown to have pan-NOTCH signaling inhibitory activity in vitro and anti-tumor efficacy in xenograft models of leukemia and triple-negative breast cancer harboring NOTCH1 and NOTCH3 activating mutations or overexpression[167]. On the basis of clinical data in non-Hodgkin lymphoma, NOTCH1 activating alterations may be associated with sensitivity to the approved PI3K inhibitor copanlisib[85]; this is further supported by limited preclinical data that suggest that NOTCH1 may be a negative regulator of PTEN[168-169]. A Phase 3 study of the GSI semagacestat for the treatment of Alzheimer's disease reported a significantly greater incidence of skin SCC when compared with placebo (5% vs 1%)[170], suggesting GSIs may not be beneficial for the treatment of skin SCC. While activating mutations may be targeted via gamma-secretase inhibitors or PI3K inhibitors, there are no therapies available to address NOTCH1 inactivation, as seen here.

FREQUENCY & PROGNOSIS

NOTCH1 mutations have been reported in 63% of cutaneous squamous cell carcinomas (CSCCs) analyzed (COSMIC, Jan 2021)[155], and in 9/12 of primary CSCC tumors in the literature[171]. Other studies of metastatic CSCC reported NOTCH1 alteration in 17% of patients[109], and in sporadic CSCC at a frequency of 45-75%[27]. One study found no correlation between NOTCH1 mutation and prognosis or clinical variables in skin SCC[109].

In contrast to the activating NOTCH1 mutations reported in T-ALL, mutations in SCC are believed to be primarily inactivating; furthermore, loss of NOTCH1 activity is thought to be a promoting event in tumorigenesis[171-176].

FINDING SUMMARY

NOTCH1 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or an oncogene[171,177]. Upon binding of membrane-bound ligands, the NOTCH1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex that regulates downstream target genes involved in cell fate determination, proliferation, and apoptosis[178-179]. NOTCH1 alterations that disrupt ligand binding[180-182], remove the ankyrin repeats (amino acids 1987-2089) and/or the transactivation domain (amino acids 2214-2376) which are necessary for NOTCH1 function, such as observed here, are predicted to be inactivating[179,183-185]. Several point mutations, including D469G, A465T, R1594Q, and P1770S, have also been reported to inactivate NOTCH1[171,186].

GENE
ROS1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

The ROS1 TKIs crizotinib[187], entrectinib[188], ceritinib[189], and lorlatinib[190-191] have shown significant clinical activity for patients with ROS1-rearranged NSCLC. Treatment with either brigatinib[192] or cabozantinib[193-196] has resulted in clinical benefit for patients with ROS1-rearranged NSCLC that developed resistance to crizotinib and ceritinib. Only ROS1 fusions have been found to result in constitutive activation of ROS1; therefore, the effectiveness of ROS1 inhibitors in the absence of ROS1 rearrangement is unclear.

FREQUENCY & PROGNOSIS

The frequency of ROS1 copy number alterations in cutaneous SCC has not been evaluated (cBioPortal, COSMIC, PubMed, May 2020)[155,197-198]. Published data investigating the prognostic implications of ROS1 alterations in cutaneous SCC are limited (PubMed, May 2020).

FINDING SUMMARY

The ROS1 oncogene encodes a tyrosine kinase of the insulin receptor family that plays a role in regulating cellular growth and differentiation by activating several signaling pathways, including those involving mitogen-activated protein kinase ERK1/2, phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), STAT3, and VAV3[199]. ROS1 has been reported to be amplified in cancer[198] and may be biologically relevant in this context[200-201]. However, only ROS1 fusions have been found to result in constitutive activation of ROS1, thereby suggesting ROS1 inhibitors may not be relevant in this case.

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GENE
TP53

ALTERATION
H179Q

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
537T>G

VARIANT ALLELE FREQUENCY (% VAF)
49.4%

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 adavosertib[202-205], or p53 gene therapy and immunotherapeutics such as SGT-53[206-210] and ALT-801[211]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[212]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[213]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[214]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[215]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[216]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[217]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[210]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[218]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[219-221]. 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% DCR[222]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[223-224]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[225-226]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 41-51% of cutaneous squamous cell carcinomas (SCCs)[227-228]. Inactivating TP53 mutations have been reported to be common in cutaneous SCC and a driver event in cutaneous SCC progression[229]. Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[230-235]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[230-231]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[236]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[234,237-238]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[239]. Alterations such as seen here may disrupt TP53 function or expression[240-244]. One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with Li-Fraumeni syndrome (ClinVar, Sep 2020)[245]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[246-248], including sarcomas[249-250]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[251] to 1:20,000[250]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[252]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Afatinib

Assay findings association

EGFR
amplification

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR activating mutations or amplification may indicate sensitivity to afatinib. In Phase 2 studies of afatinib, patients with EGFR-amplified NSCLC achieved an objective response rate of 20% (5/25) and a disease-control rate of 64% (16/25)[48], and 2/5 patients with EGFR amplification in other solid tumors experienced stable disease[49].

SUPPORTING DATA

Afatinib compared with methotrexate as second-line treatment for platinum-refractory head and neck squamous cell carcinoma (HNSCC) improved PFS (2.6 vs. 1.7 months) and OS (6.8 vs. 6.0 months)[253-254] ; the benefit of afatinib was greater in patients with p16INK4a-negative than p16INK4a-positive disease[253] and had fewer adverse events than the methotrexate treatment arm[254]. However, treatment with afatinib did not increase median DFS as compared to placebo (43.4 months vs. not estimable) in a Phase 3 trial for patients with unresected locoregionally advanced HNSCC previously treated with chemoradiotherapy[255]. In a Phase 2 study in HNSCC, afatinib demonstrated comparable antitumor activity to cetuximab (8.1% vs. 9.7% response rate) and provided clinical benefit in the group of patients previously treated with cetuximab[256]. Afatinib in combination with carboplatin and paclitaxel as induction chemotherapy achieved PRs for 5/9 and SD for 2/9 enrolled patients with locally advanced HNSCC; the maximum tolerated dose of afatinib in this combination was 20mg[257]. A Phase 2 study of neoadjuvant afatinib for treatment-naive patients with resectable HNSCC reported partial metabolic responses for 69.6% (16/23) of cases[258].

Cetuximab

Assay findings association

EGFR
amplification

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[41].

SUPPORTING DATA

A Phase 2 study of single-agent cetuximab as first-line therapy for patients with unresectable cutaneous squamous cell carcinoma (SCC) reported 2 complete responses (CRs) and 8 partial responses (PRs) out of the 36 included patients, for a disease control rate of 69%[259]. A study of cetuximab as a single agent or in combination with radiotherapy or carboplatin in 20 patients with cutaneous SCC reported a disease control rate of 78%, 9 PRs, 6 disease stabilizations, and progression in 4 patients[260]. A retrospective study reported that 3/4 patients with skin SCC treated with cetuximab experienced a CR; of these, 2 remained in remission for over 3 years[261].

Dacomitinib

Assay findings association

EGFR
amplification

AREAS OF THERAPEUTIC USE

Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical[262-264] and preclinical[265-266] data, EGFR amplification or activating mutation may indicate sensitivity to dacomitinib.

SUPPORTING DATA

A Phase 2 study of dacomitinib in patients with advanced penile squamous cell carcinoma (SCC) reported an ORR of 32% (1 CR, 8 PR), including a 100% DCR (1 CR, 1 PR, 2 SD) in four patients with EGFR amplification[264,267]. A Phase 2 study of dacomitinib in patients with recurrent or metastatic head and neck SCC reported clinical benefit (defined as PFS > 4 months) in 13/31 (42%) patients[268]. Studies of dacomitinib in esophageal[269] and cutaneous[270] SCC reported RRs of 12.5% (6/48) and 28% (12/48), respectively, but high DCR of 73% and 86%, respectively.

Erlotinib

Assay findings association

EGFR
amplification

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucirumab for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. In a prospective study of advanced NSCLC treated with gefitinib (n=102), EGFR copy gain was significantly associated with improved survival (HR=0.44)[47]. Several meta-analyses spanning 14 to 20 studies of patients with advanced NSCLC receiving single-agent erlotinib or gefitinib (n=1725 to 1854) reported the association of increased EGFR copy number with improved OS (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11)[45-46,271] .

SUPPORTING DATA

The approval of erlotinib in NSCLC is based on a Phase 3 randomized trial demonstrating prolonged overall survival for unselected NSCLC patients treated with erlotinib compared to standard chemotherapy[272]. Furthermore, several randomized Phase 3 trials have shown a significant improvement in response and progression-free survival for this class of medications compared with combination chemotherapy in patients with known EGFR mutations, including the EURTAC trial of erlotinib vs. platinum-based chemotherapy[273]. A Phase 3 clinical trial comparing erlotinib to gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer reported improved overall survival when compared to patients treated with gemcitabine alone (6.24 vs. 5.91 months)[274]. In breast cancer, erlotinib as a single therapy has been reported to have minimal efficacy[275]. A Phase 1 study of the combination therapy of erlotinib with capecitabine and docetaxel in patients with metastatic breast cancer reported an overall 67% response rate; however, the authors suggested that these results will require confirmation in larger, randomized studies[276]. A Phase 2 clinical trial of erlotinib in gastric adenocarcinoma reported no clinical responses, although there were no instances of EGFR mutation or amplification in this study group[277]. A Phase 2 study in patients with metastatic esophageal or gastroesophageal junction (GEJ) cancer reported partial responses in 8% (2/24) of patients with EGFR-positive tumors, but responses were only observed in patients with squamous cell carcinoma and not in patients with adenocarcinoma[278-279] . Erlotinib in combination with modified FOLFOX6 has shown activity in patients with metastatic or advanced esophageal or GEJ cancer, with 6.1% (2/33) and 45.5% (15/33) of evaluable patients exhibiting complete responses and partial responses, respectively[280]. A study of elderly patients with esophageal or GEJ carcinoma treated with erlotinib and radiation therapy reported an overall survival of 7.3 months[281].

Everolimus

Assay findings association

PTEN
loss exons 3-6

AREAS OF THERAPEUTIC USE

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. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

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[282]. 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[283-285] .

SUPPORTING DATA

Clinical data on the efficacy of everolimus for the treatment of cutaneous SCC are limited (PubMed, Sep 2020). Everolimus has been clinically tested in patients with several squamous cell carcinomas (SCC). A Phase 2 study of everolimus therapy has reported no objective responses in any of nine patients with refractory head and neck squamous cell carcinoma[286]. A Phase 1 trial in patients with advanced solid tumors reported that everolimus in combination with low dose weekly cisplatin showed activity in several tumor types, with 3 partial responses and prolonged stable disease observed in 5 patients out of 28 evaluable patients; one patient with oropharyngeal squamous cell carcinoma obtained stable disease after more than 6 cycles of treatments[287]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[288], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[289].

Electronically signed by Chelsea Marcus, M.D. | 22 January 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

Gefitinib

Assay findings association

EGFR
amplification

AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and progression-free survival for patients with EGFR-mutated NSCLC treated with gefitinib, compared to chemotherapy[290-296] . In a prospective study of advanced NSCLC treated with gefitinib (n=102), EGFR copy gain was significantly associated with improved survival (HR=0.44)[47]. Several meta-analyses spanning 14 to 20 studies of patients with advanced NSCLC receiving single-agent erlotinib or gefitinib (n=1725 to 1854) reported the association of increased EGFR copy number with improved OS (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11)[45-46,271] . Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant overall survival benefit from gefitinib compared to placebo (HR = 0.21)[297-298] .

SUPPORTING DATA

A Phase 2 clinical trial of gefitinib given concurrently with radiotherapy and cisplatin in 15 patients with head and neck squamous cell carcinoma (HNSCC) reported that 79% of patients experienced locoregional tumor control[299], with a trend toward significance for the relationship between EGFR amplification and tumor response (p=0.057), but no relationship between EGFR activity and tumor response (p=0.10)[299]. A Phase 3 trial of docetaxel in combination with gefitinib in 270 patients with recurrent HNSCC showed no improvement in outcome versus docetaxel plus placebo[300]. A Phase 2 clinical trial of gefitinib is patients with cervical squamous cell carcinoma or adenocarcinoma reported no objective responses, but 21% (6/28) reported stable disease[301]; in this study, response did not correlate with EGFR expression status.

Panitumumab

Assay findings association

EGFR
amplification

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[41].

SUPPORTING DATA

A Phase 2 study of single-agent panitumumab in 16 patients with cutaneous SCC reported two complete responses, three partial responses, and six patients experiencing stable disease; the authors concluded that panitumumab was safe and effective even in this extensively pretreated cohort[302].

Temsirolimus

Assay findings association

PTEN
loss exons 3-6

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

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[303-304] . Temsirolimus achieved SD for 6/7 patients with PTEN-deficient cervical carcinoma[305]. Clinical studies in renal cell carcinoma[306-307] , glioblastoma[308-309] , or endometrial cancer[310-313] 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

Clinical data on the efficacy of temsirolimus for the treatment of cutaneous SCC are limited (PubMed, Nov 2020). In the context of squamous cell carcinoma (SCC), temsirolimus has been tested primarily for head and neck squamous cell carcinoma (HNSCC), and temsirolimus in combination with the VEGF antibody bevacizumab has shown significant efficacy[314]. A study assessing temsirolimus in combination with metformin in patients with advanced solid tumors reported a partial response for one patient with HNSCC, despite disease progression after treatment with docetaxel and cisplatin and subsequent treatment with zalutumumab[315]. A Phase 1 study of temsirolimus in combination with carboplatin and paclitaxel in 18 patients with HNSCC reported a partial response rate of 22% and recommended Phase 2 testing[316]. However, a Phase 2 study of temsirolimus and erlotinib in patients with recurrent and/or metastatic, platinum-refractory HNSCC reported that this combination therapy was poorly tolerated, with the trial ending early after 50% (6/12) of patients withdrew from the study[317]. A Phase 2 study of temsirolimus in patients with recurrent or metastatic cervical carcinoma reported a partial response in 3% (1/33) of patients and stable disease in 57.6% (19/33) of patients, with mild to moderate adverse effects and no toxicities greater than grade 3[305]. In a Phase 1 study of temsirolimus and bevacizumab, 2/4 of patients with cervical squamous cell carcinoma experienced a partial response[318].

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

Electronically signed by Chelsea Marcus, M.D. | 22 January 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

GENE
EGFR

ALTERATION
amplification

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Several strategies to overcome resistance are under investigation, including next-generation EGFR TKIs and EGFR inhibitor combinations.

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Oklahoma, Pennsylvania, Indiana

NCT03829436

PHASE 1

TPST-1120 as Monotherapy and in Combination With (Nivolumab, Docetaxel or Cetuximab) in Subjects With Advanced Cancers

TARGETS
PD-1, PPARalpha, EGFR

LOCATIONS: Florida, North Carolina, Tennessee, Oklahoma, Maryland, Pennsylvania, New York, Massachusetts, Michigan, California

NCT03944941

PHASE 2

Avelumab With or Without Cetuximab in Treating Patients With Advanced Skin Squamous Cell Cancer

TARGETS
PD-L1, EGFR

LOCATIONS: Louisiana, Georgia, South Carolina, North Carolina, Tennessee, Virginia

NCT04375384

PHASE 2

Cetuximab After Immunotherapy for the Treatment of Head and Neck Squamous Cell Cancer

TARGETS
EGFR

LOCATIONS: North Carolina

NCT03783403

PHASE 1

A Study of CC-95251, a Monoclonal Antibody Directed Against SIRPα, in Subjects With Advanced Solid and Hematologic Cancers

TARGETS
CD20, EGFR, SIRP-alpha

LOCATIONS: Texas, Alabama, North Carolina, Tennessee, Oklahoma, Pennsylvania, Toronto (Canada), Arizona

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NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

LOCATIONS: London (Canada), Toronto (Canada), Kingston (Canada), Ottawa (Canada), Montreal (Canada), Regina (Canada), Saskatoon (Canada), Edmonton (Canada), Vancouver (Canada)

NCT02447419

PHASE 2

Study to Evaluate the Safety and Efficacy of Gefitinib in Subjects With EGFR Amplification Refractory Solid Tumors

TARGETS
EGFR

LOCATIONS: Seoul (Korea, Republic of)

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT03524326

PHASE 1

Testing Lenvatinib and Cetuximab in Patients With Advanced Head and Neck Squamous Cell Carcinoma and Cutaneous Squamous Cell Carcinoma

TARGETS
FGFRs, KIT, PDGFRA, RET, VEGFRs, EGFR

LOCATIONS: New Jersey, New York

NCT04163952

PHASE 1

Talimogene Laherparepvec and Panitumumab for the Treatment of Locally Advanced or Metastatic Squamous Cell Carcinoma of the Skin

TARGETS
EGFR

LOCATIONS: New Jersey

GENE
PTEN

ALTERATION
loss exons 3-6

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Florida, Louisiana, Texas

NCT03992131

PHASE 1/2

A Study to Evaluate Rucaparib in Combination With Other Anticancer Agents in Patients With a Solid Tumor (SEASTAR)

TARGETS
PARP, FGFRs, VEGFRs, TOP1

LOCATIONS: Texas, Tennessee, Massachusetts

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Tennessee, Connecticut, California

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: New York, Massachusetts, California, Saint Herblain (France), Withington (United Kingdom), Sutton (United Kingdom), London (United Kingdom), Villejuif (France), Seoul (Korea, Republic of)

NCT03830918

PHASE 1/2

Niraparib and Temozolomide in Treating Patients With Extensive-Stage Small Cell Lung Cancer With a Complete or Partial Response to Platinum-Based First-Line Chemotherapy

TARGETS
PARP

LOCATIONS: California

NCT03502733

PHASE 1

Copanlisib and Nivolumab in Treating Patients With Metastatic Solid Tumors or Lymphoma

TARGETS
PI3K, PD-1

LOCATIONS: Texas, Maryland

NCT03842228

PHASE 1

Copanlisib, Olaparib, and Durvalumab in Treating Patients With Metastatic or Unresectable Solid Tumors

TARGETS
PI3K, PD-L1, PARP

LOCATIONS: Texas, Massachusetts

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, New Jersey, New York

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.

ABL1
G886V

BRIP1
S230L

FGFR3
rearrangement

FLCN
N184K

NOTCH2
S1427N

PRDM1
amplification

SETD2
Y555S

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*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*	*NSD3 (WHSC1L1)*	*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*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

Electronically signed by Chelsea Marcus, M.D. | 22 January 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. 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. 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. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics

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of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

MR Suite Version 2.1.0

The median exon coverage for this sample is 915x

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

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