PATIENT
DISEASE Lung adenocarcinoma
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

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

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
EGFR L858R	Gilotrif® (Afatinib) Iressa® (Gefitinib) Tagrisso® (Osimertinib) Tarceva® (Erlotinib)

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

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

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

Microsatellite status MS-Stable §
Tumor Mutational Burden 24 Muts/Mb §
ARFRP1 amplification §
ARID1A Y471*
ARID1A Q944*
CDK12 Q1050*
CDKN2A loss §
CDKN2B loss §
EGFR A289V
MTAP loss §
PIK3CA E453K
PIK3CA M1043I

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

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

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

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

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FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

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

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

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

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

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

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

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Biomarker Findings

Tumor Mutational Burden - 24 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

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

EGFR A289V, L858R
PIK3CA E453K, M1043I
ARID1A Q944*, Y471*
ARFRP1 amplification - equivocal†
CDK12 Q1050*
CDKN2A/B loss
MTAP loss

7 Disease relevant genes with no reportable alterations: ***ALK, BRAF, ERBB2, KRAS, MET, RET, ROS1***

† See About the Test in appendix for details.

14 Therapies with Clinical Benefit
0 Therapies with Lack of Response
37 Clinical Trials

BIOMARKER FINDINGS

Tumor Mutational Burden - 24 Muts/Mb

10 Trials *see p. 18*

Microsatellite status - MS-Stable

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Atezolizumab	1	Avelumab
Durvalumab	1	Cemiplimab
Pembrolizumab	1	
Nivolumab	2A	

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 - A289V, L858R	Afatinib 1	none
	Dacomitinib 1	
	Erlotinib 1	
	Gefitinib 1	
	Osimertinib 1	
10 Trials *see p. 22*		
PIK3CA - E453K, M1043I	none	Alpelisib
		Everolimus
		Temsirolimus
10 Trials *see p. 24*		
ARID1A - Q944*, Y471*	none	none
8 Trials *see p. 20*		

1 *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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.

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BIOMARKER

Tumor Mutational Burden

RESULT
24 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[1-3] and anti-PD-1 therapies[1-4]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb; similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb[1-2,5-15]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[16], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[17], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[18]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[19]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[20-21], several other large studies did find a strong association with increased TMB[22-25]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[26]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[20]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[27]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[27-28].

FINDING SUMMARY

Tumor mutational 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[5,31], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[32-36], and microsatellite instability (MSI)[32,35-36]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-2,5-15,19,37-45].

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[46-48], including approved therapies nivolumab and pembrolizumab[49]. 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)[50].

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[51-56], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[57-60]. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Feb 2020). One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[51].

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[61]. 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[61-63]. 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[64-66]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[61,63,65-66].

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GENE
EGFR

ALTERATION
A289V, L858R

TRANSCRIPT NUMBER
NM_005228

CODING SEQUENCE EFFECT
- 866C>T
- 2573T>G

POTENTIAL TREATMENT STRATEGIES

EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[67], gefitinib[68], afatinib[69], dacomitinib[70], and osimertinib[71]. Third-generation EGFR inhibitors, such as osimertinib, selectively target mutated EGFR, including EGFR T790M[71-72]. Osimertinib achieved an ORR of 61% in T790M-positive cases and 21% in T790M-negative cases[71]. Resistance to EGFR inhibition may arise by reactivation of the MAPK pathway, and preclinical evidence suggests that co-targeting EGFR and MAPK signaling may retard the development of acquired resistance to third-generation EGFR inhibitors[73-75]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin[76-77] that has also shown benefit in patients with CRC and melanoma[78-79]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy[80-83]. Preclinical studies have reported that EGFR-mutant cells[80-82], including cells with exon 20 insertions[84], are sensitive to HSP90 inhibitors. For patients with EGFR exon 19 deletion/ L858R-positive and T790M- negative NSCLC who had previously progressed on first or second generation EGFR TKIs, a Phase 1 study evaluating the HER3-targeted antibody U3-1402 reported tumor reduction in 12 patients with 2 confirmed PRs (2/13)[85]. 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[86-87]. In a Phase I/II 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[88]. The reovirus Reolysin targets cells with activated RAS signaling[89-91] 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[92-100]. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear[101]. For patients with NSCLC treated with EGFR tyrosine kinase inhibitors, PIK3CA mutation is associated with shorter OS in a meta-analysis (pooled HR of 1.83)[102]. Clinical studies of lung cancer have shown that acquired PIK3CA mutation may confer resistance to EGFR inhibitors like osimertinib[103-104] . The Phase 3 IMpower study showed that the addition of atezolizumab to bevacizumab plus chemotherapy treatment also had clinical efficacy in patients with untreated EGFR-mutated or ALK-rearranged metastatic NSCLC[105]; therefore, the patient's clinical context should be considered.

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[24,106-107] and in 4% of lung squamous cell carcinomas[108]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[109-114]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[115-116]. In lung adenocarcinoma, EGFR gene amplification was a predictor of poor disease-free survival in all patients and of poor overall survival in patients with EGFR mutations[117-118]. Nuclear expression of EGFR in NSCLC has been reported to associate with higher disease stage, shorter progression-free survival, and shorter overall survival[119]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[120] or resected Stage 1 NSCLC[121].

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[122]. EGFR L858 is located in the kinase domain and is encoded by exon 21; mutations at this position including L858R[123-125] and L858Q[126] have been characterized as activating. Patients with the L858R mutation have been shown to be sensitive to EGFR tyrosine kinase inhibitors, such as erlotinib, gefitinib[123-125], and afatinib[127]. Other mutations at this position are predicted to be activating. The EGFR A289V mutation, located in the extracellular domain, has been shown to be activating[128]. Glioblastoma cell lines harboring an EGFR A289V or A289D mutation were shown to be dependent on EGFR kinase activity[129], and other mutations at this position are also likely activating. In addition, A289V is frequently associated with increased EGFR gene copy number[128].

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GENE
PIK3CA

ALTERATION
E453K, M1043I

TRANSCRIPT NUMBER
NM_006218

CODING SEQUENCE EFFECT
- 1357G>A
- 3129G>A

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[130-131]. 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[132-137]. 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 PRs, 8/14 SDs)[138]. The pan-PI3K inhibitor buparlisib has shown limited activity as monotherapy against PIK3CA-mutated tumors[139-142]. A Phase 2 study of buparlisib in NSCLC did not meet its primary endpoint (ORR of 3% [2/63]), despite preselecting for patients with PI3K-pathway activated tumors[142]. PI3K-alpha-selective inhibitors such as alpelisib or PI3K-beta-sparing inhibitors such as taselisib may have bigger therapeutic windows than pan-PI3K inhibitors[131]. In PIK3CA-mutated advanced solid tumors, alpelisib and taselisib have achieved low ORRs (0% [0/55] to 6% [7/111]) but a high DCR (55% [36/55] to 58% [64/111])[143]. AKT inhibitors ipatasertib and capivasertib have also been tested in breast cancer. Two Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR = 0.44) or capivasertib (9.3 vs. 3.7 months, HR = 0.30) to paclitaxel in metastatic triple-negative breast cancer harboring PIK3CA/AKT1/PTEN alterations, compared with paclitaxel and placebo[144]. Responses to capivasertib were also reported in 20% (3/15) of patients with PIK3CA-mutated breast cancer in an earlier study[145]. However, a Phase 1 trial reported no PFS benefit for patients with PIK3CA-mutated, ER+/HER2- metastatic breast cancer from the addition of capivasertib to paclitaxel compared with paclitaxel plus placebo (10.9 vs. 10.8 months)[146]. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[147-151]. For patients with NSCLC treated with EGFR tyrosine kinase inhibitors, PIK3CA mutation is associated with shorter OS in a meta-analysis (pooled HR of 1.83)[102]. Clinical studies of lung cancer have shown that acquired PIK3CA mutation may confer resistance to EGFR inhibitors like osimertinib[103-104] .

FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3CA mutation was observed in 8.2% of lung adenocarcinoma cases[152] and in 15.7% of lung squamous cell carcinoma cases[108]. Studies have observed PIK3CA amplification and mutation to be far more frequent in lung squamous cell carcinomas than in lung adenocarcinomas, with amplification reported in 34-42% of the former[153-156]. The prognostic significance of PIK3CA mutation or overexpression in NSCLC is unclear, with several studies reporting contradictory data, which may be influenced by the specific PIK3CA mutation, histologic subtype, and the presence of concurrent mutations in oncogenes such as EGFR and KRAS[157-162].

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[163-164]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[165-183].

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GENE
ARID1A

ALTERATION
Q944*, Y471*

TRANSCRIPT NUMBER
NM_006015

CODING SEQUENCE EFFECT
- 2830C>T
- 1413C>G

POTENTIAL TREATMENT STRATEGIES

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620; 1 patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[184-185]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to inhibitors of EZH2[186-187], which are under investigation in clinical trials. Other studies have reported that loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[188-190]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy in patients with ovarian clear cell carcinoma[191-192] and to 5-fluorouracil (5-FU) in CRC cell lines[193].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma (CRC), and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2020)[194-199]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[200-203], CRC[204-206], and gastric cancer[207-211]. ARID1A protein loss is associated with tumors of poor histological grade for many tumor types, including colorectal cancer (CRC)[204-206], cervical cancer[212-213], gastric cancer[207-211], urothelial carcinoma[214-216], ovarian and endometrial cancers[192,200-203,217-221], breast carcinoma[222-224], and clear cell renal cell carcinoma[225]. However, prognostic data regarding patient survival are often mixed and conflicting.

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[195,210,223,226-231]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[195,208,227-228,232], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
ARFRP1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies available to address alterations in ARFRP1. Amplification of ARFRP1 has been reported to be significantly associated with the amplification of potential cancer drivers such as AURKA and the CCN (cyclin) genes[233], but it is not known whether amplification of ARFRP1 in this context has therapeutic relevance.

FREQUENCY & PROGNOSIS

ARFRP1 mutations are rare across tumor types (<1%), whereas ARFRP1 amplification has been reported at high frequency, particularly in pancreatic cancer (24%), endometrial carcinosarcoma (16%), ovarian serous carcinoma (7-15%), colorectal adenocarcinoma (7%), and gastric, lung, breast, and esophageal carcinomas (6-7% each) (COSMIC, cBioPortal, 2020)[35,234-235]. However, the implications of ARFRP1 amplification for cancer prognosis have not been evaluated in published studies (PubMed, 2020).

FINDING SUMMARY

ARFRP1 encodes ADP-ribosylation factor-related protein 1, a small GTPase involved in vesicular transport[236-237]. ARFRP1 is reportedly essential for the trafficking of several proteins, including ARL1, E-cadherin, and IGF1[238-240]. A single nucleotide polymorphism affecting ARFRP1 has been significantly associated with a risk of developing glioma by one study[241]. Although ARFRP1 has important roles in normal metabolism and hepatic and intestinal functions[240,242-243], it has not been studied extensively in the context of cancer.

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GENE
CDK12

ALTERATION
Q1050*

TRANSCRIPT NUMBER
NM_016507

CODING SEQUENCE EFFECT
3148C>T

POTENTIAL TREATMENT STRATEGIES

CDK12 inactivation in cancer is associated with genomic instability characterized by tandem duplications[244-248] and has been shown to increase tumor immunogenicity in advanced prostate cancer[245]. On the basis of preclinical and early clinical evidence in advanced prostate cancer, CDK12 inactivation may predict benefit from immune checkpoint inhibitors[245]. Retrospective studies have observed clinical benefit for patients with CDK12-mutated castration-resistant prostate cancer treated with anti-PD-1 immunotherapy[245]. Preclinical studies suggest that CDK12 truncations and inactivating mutations that affect the kinase domain (amino acids 719-1051) impair homologous recombination and sensitize cells to PARP inhibitors[249-254]. A patient with ovarian cancer and a CDK12 frameshift mutation experienced a PR to rucaparib[255]. However, multiple clinical studies have observed no responses in patients with CDK12-altered CRPC treated with PARP inhibitors[256-258] , and the relationship between CDK12 alterations and PARP inhibitor sensitivity in other disease contexts is unclear. Cells lacking CDK12 incur spontaneous DNA damage and exhibit heightened sensitivity to DNA-damaging agents[249-254].

FREQUENCY & PROGNOSIS

CDK12 mutations have been reported in 3% of lung adenocarcinoma and lung squamous cell carcinoma samples[9,152]. Published data investigating the prognostic implications of CDK12 alteration in non-prostate cancers are limited (PubMed, Mar 2020). A retrospective analysis of prostate cancer found that CDK12 alterations were associated with shorter time to metastasis and earlier development of castration-resistant disease[259].

FINDING SUMMARY

CDK12 encodes a cyclin-dependent kinase that interacts with cyclin K to regulate the phosphorylation of RNA polymerase II and the expression of genes involved in maintaining genomic stability, including BRCA1 and ATR[260]. CDK12 alterations that disrupt critical protein domains, as observed here, are predicted to be inactivating[252,261-263].

GENE
CDKN2A/B

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[264-267]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[268-269], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[270-276]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[277-278], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[107]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[108]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples[108,279-284]. In patients with lung SCC, loss of CDKN2B associated with poor survival in one study[285]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[281,286-288].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[289-290]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[280,291]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[292-293]. This alteration is predicted to result in p16INK4a[294-315] loss of function. This alteration is predicted to result in p14ARF[298,315-318] loss of function. The CDKN2B alteration is predicted to inactivate p15INK4b[319].

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GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

Inactivation of MTAP is being explored for specific metabolic vulnerabilities. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, providing competition to purine poisons lacking in MTAP-deficient cells[320-328]. However, such combination approaches are not being clinically tested, and a Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy in 65 patients with MTAP-deficient cancers reported no responses and stable disease in 24% of patients[329]. Other approaches have been described in preclinical studies[330-332], but these have not been clinically tested.

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[333-334]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[335], gastrointestinal stromal tumors[336], mantle cell lymphoma (MCL)[337], melanoma[338-339], gastric cancer[340], myxofibrosarcoma[341], nasopharyngeal carcinoma[342], ovarian carcinoma[333] and non-small cell lung cancer[343]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[344] or in astrocytoma[345]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[346], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[347].

Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[348-349], esophageal cancer[350-351], osteosarcoma[352], and CRC[353].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[354-355]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[335,356-357], thereby reducing intracellular arginine methylation[330-332] and altering cell signaling[357-358]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

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Afatinib

Assay findings association

EGFR
A289V, L858R

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.

GENE ASSOCIATION

EGFR activating mutations or amplification may indicate sensitivity to afatinib. Extensive clinical evidence has demonstrated that treatment with afatinib, when compared with chemotherapy, increases PFS for patients with EGFR-mutated NSCLC[69,359] . In a Phase 3b trial, first-line afatinib enabled an ORR and DCR of 45.9% (220/479) and 86.0% (412/479), respectively, for patients with EGFR-mutated NSCLC[360].

SUPPORTING DATA

Afatinib has shown significant clinical activity for patients with NSCLC and the EGFR common sensitizing mutations L858R or exon 19 deletions, based on extensive clinical evidence[69,359,361-364] . Two randomized Phase 3 trials reported significantly improved median PFS from afatinib compared with chemotherapy for patients with EGFR common sensitizing mutations (LUX-Lung 3, 13.6 vs. 6.9 months, HR 0.47, p<0.001; LUX-Lung 6, 11.0 vs. 5.6 months, HR 0.28, p<0.0001)[69,359] . However, while afatinib significantly increased OS relative to chemotherapy for patients with EGFR exon 19 alterations in these two trials (LUX-Lung 3, 33.3 vs. 21.1 months, HR=0.54; LUX-Lung 6, 31.4 vs. 18.4 months, HR=0.64), no significant OS differences were observed in treatment for patients with L858R mutation[127]. A similar alteration-specific difference was observed for EGFR-mutated treatment-naive NSCLC in a retrospective analysis, which reported numerically longer median OS from second- versus first-generation EGFR TKIs (48.8 vs. 26.4 months, HR=0.59) for patients with exon 19 deletions, but no substantial difference for patients with L858R (25.4 vs. 20.6 months, HR=0.90)[361]. A Phase 2b study of first-line afatinib compared with gefitinib, also for NSCLC with exon 19 deletions or L858R, reported similar median OS for the two therapies (27.9 vs. 24.5 months, HR=0.86) but significantly longer time-to-treatment-failure (13.7 vs. 11.5 months, HR=0.75) and higher ORR (73% vs. 56%, p=0.0018) with afatinib[362]. Patients with metastatic NSCLC and common EGFR mutations who progressed on prior chemotherapy experienced an ORR of 50.0% (30/60) from afatinib in a Phase 4 trial[363]. As first-line therapy for NSCLC with EGFR exon 19 deletions or L858R, prospective or randomized Phase 2 trials have reported a median PFS of 10.2 months and OS of 24.8 months for patients unfit for chemotherapy[364] and an ORR of 72.5% (n=40, 1 CR), DCR of 100% (40/40), and median PFS and OS of 15.2 and 30.0 months, respectively, for elderly patients ≥70 years old[365]. A retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 27.4% (63/230) for patients with common sensitizing EGFR mutations and an ORR of 24.4% (105/431) for the entire cohort[366]. In a case report, a patient with NSCLC with exon 19 deletion and leptomeningeal metastases experienced an ongoing 16-month PR from afatinib in extracranial, brain, and leptomeningeal lesions[367]. For patients with erlotinib- or gefitinib-resistant NSCLC and EGFR mutations, Phase 2/3 studies of afatinib treatment have generally reported ORRs of only 7 to 9%[368-373] ; however, DCRs of more than 50% have been observed[372]. In a Phase 1b or observational study, patients with EGFR-mutated NSCLC who progressed on afatinib experienced further clinical benefit from subsequent treatment with afatinib and cetuximab[374] or osimertinib[375], respectively. Extensive clinical data have demonstrated that afatinib is effective for patients with EGFR-mutated advanced NSCLC, including exon 19 deletions and L858 mutations, as well as uncommon sensitizing mutations in exons 18 or 20[69,127,359,362,364,366,376] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[372,377-385] . The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma reported significantly longer median OS (7.9 vs. 6.8 months, HR=0.81), significantly longer median PFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[376]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[386].

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Atezolizumab

Assay findings association

Tumor Mutational Burden
24 Muts/Mb

AREAS OF THERAPEUTIC USE

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 non-small cell lung cancer (NSCLC) and patients with either PD-L1-positive or -negative urothelial carcinoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, or PD-L1-positive triple-negative breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In the first-line setting, the Phase 3 IMpower130, IMpower150, and IMpower132 studies have shown that the addition of atezolizumab to chemotherapy-based regimens significantly improves survival for patients with non-squamous NSCLC without EGFR or ALK alterations[105,387-388] . In IMpower130, median PFS (7.0 vs. 5.5 months, HR=0.64) and median OS (18.6 vs. 13.9 months, HR=0.79) were significantly improved with atezolizumab plus nab-paclitaxel and carboplatin relative to chemotherapy alone; benefit was observed irrespective of PD-L1 status[387]. Similarly, IMpower150 reported improved median PFS (8.3 vs. 6.8 months, HR=0.62) and median OS (19.2 vs. 14.7 months, HR=0.78) with the addition of atezolizumab to bevacizumab, paclitaxel, and carboplatin; longer PFS was observed irrespective of PD-L1 status or KRAS mutation[105]. In IMpower132, the addition of atezolizumab to first-line carboplatin or cisplatin with pemetrexed in non-squamous NSCLC increased median PFS (7.6 vs. 5.2 months, HR=0.60) relative to chemotherapy alone[388]. The Phase 3 OAK trial comparing atezolizumab to docetaxel for patients with previously treated non-small cell lung carcinoma (NSCLC) reported a significant increase in median OS (13.8 vs. 9.6 months) and duration of response (DOR; 16.3 vs. 6.2 months)[389], confirming previous Phase 2 trial data[390-391]. Similar benefit was observed for patients with squamous or non-squamous histology (HR=0.73 for either group); clinical benefit was observed regardless of PD-L1 status, although greater benefit was achieved with tumor PD-L1 expression >50% (HR=0.41) compared with <1% (HR=0.75)[389]. Retrospective analysis of the OAK trial revealed numerically improved ORR in patients receiving concomitant atezolizumab and metformin compared with atezolizumab alone (25% vs. 13%), but no difference in PFS or OS with the addition of metformin[392].

Dacomitinib

Assay findings association

EGFR
A289V, L858R

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.

GENE ASSOCIATION

On the basis of clinical[70,393-394] and preclinical[395-396] data, EGFR amplification or activating mutation may indicate sensitivity to dacomitinib. Patients with untreated advanced NSCLC and EGFR L858R mutations achieved an ORR of 73% (68/93)[393] and a median OS of 32.5 months with dacomitinib[70].

SUPPORTING DATA

A randomized Phase 3 trial in patients with NSCLC with activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS, 34.1 vs. 26.8 months, HR=0.760; median PFS, 14.7 vs. 9.2 months, HR=0.59)[393,397] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[398]. A pooled subgroup analysis of patients with NSCLC with activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (median PFS, 14.6 vs, 9.6 months, HR=0.717; median OS, 26.6 vs, 23.2 months, HR=0.737)[399]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[400-402] . A Phase 2 study of dacomitinib in patients with NSCLC who had been previously treated with chemotherapy or erlotinib and were not selected for EGFR mutations reported an ORR of 4.5% (3/66)[401]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[403].

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Durvalumab

Assay findings association

Tumor Mutational Burden
24 Muts/Mb

AREAS OF THERAPEUTIC USE

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 urothelial carcinoma, non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In a Phase 2 ATLANTIC study, patients with NSCLC exhibiting tumor cell PD-L1 expression ≥25% who were negative for EGFR mutation or ALK rearrangement were more likely to benefit from durvalumab monotherapy than those whose tumor either harbored an EGFR mutation or harbored an ALK rearrangement (ORR 21.0% vs. 12.2%), although survival was not significantly different between the cohorts[404]. Studies evaluating durvalumab in combination with EGFR inhibitors for patients with NSCLC harboring EGFR alterations reported an ORR of 43.5% and median duration of response (mDOR) of 20.4 months, but with increased toxicity, for the combination with osimertinib in the Phase 3 TATTON study[405]; an ORR of 64.3% (9/14) with mDOR of 21.4 months for the combination with osimertinib, versus ORR of 80.0% (12/15) with DOR of 17.5 months for osimertinib monotherapy in the Phase 3 CAURAL study[406]; and an ORR of 63.3% and median PFS of 10.1 months for the combination with gefitinib[407]. In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable NSCLC who did not have progression on chemoradiotherapy (CT), durvalumab monotherapy was superior to placebo, including for median PFS (mPFS) (17.2 vs. 5.6 months, HR=0.51), median OS (mOS) (HR=0.68, p=0.0025) and ORR (30.0% vs. 17.8%, p<0.001)[408]. Superior OS elicited by durvalumab monotherapy in EGFR/ALK-negative metastatic NSCLC with tumor cell PD-L1 expression ≥25% was also reported in the Phase 3 MYSTIC trial for treatment-naive patients in comparison to CT (HR=0.63)[409] and in the Phase 3 ARCTIC study for patients with 2 or fewer prior therapies in comparison with standard of care (HR=0.63; 11.7 months vs. 6.8 months)[410]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[404,411] and OS[411] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90% tumor cells with PD-L1 staining) had an ORR of 30.9% (21/68), compared with ORRs of 16.4% (24/146) for patients with ≥25% of tumor cells and 7.5% (7/93) for patients with <25% of tumor cells with PD-L1 staining, respectively[404]. Retreatment with durvalumab in patients with PD-L1-positive (≥25%), EGFR/ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or an SD for 25.0% (10/40) of patients[412]. Durvalumab in combination with nab-paclitaxel for patients with previously treated advanced NSCLC elicited mPFS of 4.5 months and an ORR of 27%[413], whereas a combination with tremelimumab and durvalumab elicited an ORR of 18.8% (40/213) for patients with non-squamous NSCLC[414] and improved OS versus CT for patients with NSCLC with tumor cell PD-L1 expression ≥25% (HR=0.64)[409].

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Erlotinib

Assay findings association

EGFR
A289V, L858R

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved both as first-line and maintenance therapy, as well as second or greater line of treatment after chemotherapy failure, 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.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. In patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[415]. A heavily pretreated patient with KRAS wild-type metastatic pancreatic ductal adenocarcinoma and an EGFR exon 19 deletion experienced a sustained partial response for 32 weeks to erlotinib monotherapy[416].

SUPPORTING DATA

The initial approval of erlotinib to treat patients with NSCLC was based on the Phase 3 BR.21 trial, which demonstrated prolonged OS for genomically unselected patients treated with erlotinib compared with those treated with standard chemotherapy[417]. For patients with EGFR-mutated NSCLC, the Phase 3 EURTAC trial reported improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37)[67]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[418]. Meta-analysis of studies comparing erlotinib or gefitinib versus chemotherapy in the first-line setting reported no significant improvement in OS for patients with EGFR-mutated NSCLC; however, the lack of improved OS was attributed to the effectiveness of postprogression salvage therapy[419]. In the maintenance setting, the placebo-controlled Phase 3 SATURN trial reported significantly improved PFS with maintenance erlotinib following first-line platinum-based chemotherapy irrespective of EGFR status; however, the largest effect was seen for patients with EGFR mutations (HR=0.10)[420]. In the neoadjuvant setting, a Phase 2 trial reported a numerically improved ORR and significantly longer PFS with erlotinib compared with chemotherapy for patients with advanced EGFR-mutated NSCLC[421]. In the placebo-controlled Phase 3 RELAY trial, the addition of ramucirumab to erlotinib improved PFS for previously untreated patients with NSCLC harboring EGFR L858R or exon 19 deletion (19.4 vs. 12.4 months, HR=0.59)[422]. In a Phase 2 trial, no clinical benefit was observed from the addition of bevacizumab to erlotinib for patients with NSCLC harboring EGFR exon 19 deletion or L858R mutation[423].

Gefitinib

Assay findings association

EGFR
A289V, L858R

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.

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[415,424-429] .

SUPPORTING DATA

A Phase 3 trial of first-line gefitinib therapy for patients with NSCLC and EGFR exon 19 deletions or L858R mutations reported a longer PFS (9.2 months vs. 6.3 months)[426] but no change in median OS (34.9 months vs. 37.2 months) compared with patients treated with cisplatin plus docetaxel (median OS of 37.2 months)[430]. Gefitinib achieved an ORR of 69.8% and an OS of 19.2 months as first-line treatment for Caucasian patients with non-small cell lung carcinoma (NSCLC) and EGFR sensitizing mutations[68]. In the retrospective analysis of a Phase 3 study for East Asian patients, gefitinib was reported to have a longer PFS for patients with EGFR mutation-positive NSCLC compared with carboplatin/paclitaxel doublet chemotherapy[427,431] . Two Phase 3 trials of gefitinib plus pemetrexed and carboplatin compared with gefitinib alone for patients with advanced NSCLC harboring EGFR activating mutations reported significantly higher ORRs (75.3% and 84% vs. 62.5% and 67%), longer median PFSs (16 and 20.9 months vs. 8 and 11.9 months), and longer median OSs (50.9 months and not reached vs. 17 and 38.8 months) with combination treatment; however, combination treatment was associated with increased Grade 3 or higher adverse events[432-433] . Retrospective analysis of East Asian patients with advanced NSCLC receiving first-line gefitinib therapy reported that patients with EGFR exon 19 mutations experienced a longer median PFS (10.9 months) compared with patients with EGFR mutations in exon 18 (7.9 months), exon 20 (1.2 months), exon 21 (7.7 months), or double mutations (5.7 months); however, no differences in OS were seen between EGFR mutations[434]. In a Phase 1 study for treatment-naive patients with NSCLC, best ORRs of 78% (7/9) were observed in patients treated with combination gefitinib and the PD-L1 inhibitor durvalumab as first-line treatment and of 80% (8/10) in those treated with the combination after gefitinib monotherapy[435].

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Nivolumab

Assay findings association

Tumor Mutational Burden
24 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, hepatocellular carcinoma (HCC), classical Hodgkin lymphoma (cHL), and metastatic small cell lung cancer (SCLC). Furthermore, nivolumab is approved as both a single agent and in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In patients with advanced non-small cell lung cancer (NSCLC) and at least 5% PD-L1 expression, although first-line nivolumab did not improve median PFS (4.2 vs. 5.9 months, HR=1.15) or OS (14.4 vs. 13.2 months, HR=1.02) in the overall population as compared with investigator's choice of platinum-based doublet chemotherapy, patients with elevated TMB (TMB ≥13 muts/Mb) experienced more benefit from nivolumab than from chemotherapy (PFS of 9.7 vs. 5.8 months, ORR of 47% vs. 28%)[8]. A study of neoadjuvant nivolumab for patients with resectable NSCLC reported that major pathologic responses occurred in 45.0% (9/20) of patients and significantly correlated with TMB[12]. For patients with platinum-refractory non-squamous non-small cell lung cancer (NSCLC), ¬nivolumab improved median OS (12.2 vs. 9.4 months) and ORR (19% vs. 12%) compared with docetaxel in the Phase 3 CheckMate 057 study; PD-L1 expression was associated with OS benefit from nivolumab in this study (HR=0.40–0.59)[436]. In advanced squamous NSCLC, second-line nivolumab resulted in longer median OS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel in the Phase 3 CheckMate 017 study; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[437-438] . Pooled analysis of CheckMate 057 and CheckMate 017 showed improved long-term OS and PFS benefit for nivolumab over docetaxel, with 5-year OS rates of 13.4% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[439]. Combination of nivolumab with the CTLA4-targeting antibody ipilimumab improved median OS for patients with advanced NSCLC relative to chemotherapy regardless of PD-L1 positivity or TMB status (17.1 vs. 13.9 months, HR=0.73) in the Phase 3 CheckMate 227 study[17], despite earlier analysis of this trial which suggested improved PFS only for patients with TMB ≥10 muts/Mb[10]. In another arm of the CheckMate 227 study, combination of nivolumab with platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[440], despite Phase 1 results in the same setting suggesting improved ORR and OS[441].

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Osimertinib

Assay findings association

EGFR
A289V, L858R

AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR TKI that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved as first-line treatment for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations as well as to treat patients with metastatic EGFR T790M-positive NSCLC and disease progression on or after EGFR TKI therapy.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations and/or the EGFR T790M mutation may predict sensitivity to osimertinib[71-72,442] . T790M-positive patients showed higher response rates than T790M-negative cases in a Phase 1 study for patients with acquired EGFR TKI resistance (61% vs. 21%)[71]. Patients with untreated advanced NSCLC and EGFR exon 19 deletions or L858R mutations achieved an ORR of 80% and a median PFS of 21.4 and 14.4 months, respectively[72].

SUPPORTING DATA

The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months; HR=0.80) for patients with advanced NSCLC and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858)[72,443] . A Phase 1 study reported that T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and median PFS of 2.8 months[71]. A Phase 2 study of osimertinib for EGFR-TKI-naïve patients with metastatic or recurrent NSCLC and uncommon EGFR mutations reported a 50.0% (18/36) ORR and an 88.9% (32/36) DCR with a median PFS of 8.2 months and a median duration of response of 11.2 months; patients harboring L861Q, G719X, or S768I mutations had ORRs of 77.8% (7/9), 52.6% (10/19), and 37.5% (3/8), respectively[444]. A Phase 1b study in TKI-pretreated NSCLC patients combined osimertinib with the immunotherapy durvalumab or MET inhibitor savolitinib and observed PRs for each of the combinations (9/14 PRs with durvalumab and 6/11 PRs with savolitinib)[445]. This same study also combined osimertinib with the MEK inhibitor selumetinib and reported a 37% ORR and 67% DCR (31/83 PRs, 25/83 SDs) with a median duration of response of 9.1 to 16.6 months depending on dosage; 67% of patients harbored an EGFR exon 19 deletion[446].

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Pembrolizumab

Assay findings association

Tumor Mutational Burden
24 Muts/Mb

AREAS OF THERAPEUTIC USE

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 for patients with microsatellite instability-high (MSI-H) or mismatch-repair-deficient (dMMR) solid tumors, MSI-H or dMMR colorectal cancer (CRC) that has progressed on specific therapies, or PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin lymphoma, cervical cancer, gastric cancer, esophageal cancer, or gastroesophageal junction (GEJ) carcinoma. It is also approved in various treatment settings for patients with melanoma, NSCLC, small cell lung cancer, HNSCC, urothelial carcinoma, hepatocellular carcinoma, or Merkel cell carcinoma. Combination treatments with pembrolizumab are approved for patients with NSCLC, renal cell carcinoma, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

For TKI-naive patients with EGFR-mutated PD-L1-positive NSCLC (73.0% with PD-L1 expression ≥50.0%), pembrolizumab monotherapy did not elicit any responses (ORR of 0.0%, 0/10) in a Phase 2 study, thereby suggesting lack of efficacy in this population[447]. The superiority of pembrolizumab over platinum chemotherapy for the first-line treatment of patients with PD-L1-positive NSCLC lacking EGFR or ALK alterations was demonstrated in the Phase 3 KEYNOTE-042 and -024 studies, which reported improved median OS (mOS) for PD-L1 tumor proportion scores (TPS) ≥1% (16.7 vs. 12.1 months, HR=0.81)[448] and ≥50% (20.0–30.0 vs. 12.2–14.2 months, HR=0.63-0.69)[448-449] . In the Phase 1b KEYNOTE-100 study of pembrolizumab, mOS was numerically higher for patients with NSCLC and PD-L1 TPS ≥50% relative to those with lower levels of expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[450]. A retrospective study showed that among patients with NSCLC and high PD-L1 expression treated with first-line pembrolizumab, mOS was improved for patients with TPS 90% to 100% relative to those with TPS 50% to 89% (not reached vs. 15.9 months, HR=0.39)[451]. Phase 3 studies showed that the addition of pembrolizumab to chemotherapy is superior to chemotherapy alone in the first-line setting for patients with either non-squamous (KEYNOTE-189)[452] or squamous (KEYNOTE-407)[453] NSCLC, regardless of PD-L1 status. For the first-line treatment of patients with NSCLC and high PD-L1 expression (TPS ≥50%), a meta-analysis of KEYNOTE-024 and -189 reported the combination of pembrolizumab and chemotherapy to be non-superior to pembrolizumab alone in terms of survival benefit; however, the combination did increase ORR (+21.5%, p=0.011)[454]. In the Phase 2/3 KEYNOTE-010 study, pembrolizumab extended mOS relative to docetaxel (10.4–12.7 vs. 8.2 months) for patients with previously treated PD-L1-positive NSCLC[455]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single-agent and in combination with chemotherapy, for the treatment of patients with NSCLC and brain metastases[456-458] . Clinical activity has also been achieved with pembrolizumab in combination with ipilimumab[459], the HDAC inhibitor vorinostat[460], and the multikinase inhibitor lenvatinib[461].

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Alpelisib

Assay findings association

PIK3CA
E453K, M1043I

AREAS OF THERAPEUTIC USE

Alpelisib inhibits phosphatidylinositol-3-kinase (PI3K) with selective activity against the alpha isoform (PI3K-alpha). Alpelisib is FDA approved in combination with fulvestrant for postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated advanced breast cancer following progression on or after endocrine therapy.

GENE ASSOCIATION

On the basis of prospective clinical data, PIK3CA mutations including C420R, E542K, E545A, E545G, E545K, E545D, Q546E, Q546R, H1047L, H1047Y, and H1047R are associated with sensitivity to alpelisib. In ER+/HER2– breast cancer, PFS benefit from the addition of alpelisib to fulvestrant was specifically observed for patients with PIK3CA mutations (11.0 vs. 5.7 months, HR=0.65), including patients with PIK3CA exon 9 or exon 20 mutations[130]. Objective responses have also been achieved by patients with several other solid tumor types harboring PIK3CA mutation[143,462] .

SUPPORTING DATA

Clinical data on the efficacy of alpelisib for the treatment of lung cancer are limited (PubMed, Jan 2020). Alpelisib has been primarily studied in breast cancer. In the prospective Phase 3 SOLAR-1 study, addition of alpelisib to fulvestrant improved the ORR (26.6% vs. 12.8%) and median PFS (11.0 vs. 5.7 months, HR=0.65) for patients with ER+/HER2– endocrine-therapy-resistant breast cancer harboring PIK3CA mutation[130]. A Phase 1 trial for ER+/PIK3CA-mutated breast cancer found that the combination of alpelisib and aromatase-inhibitor treatment improved PFS for patients with multiple PIK3CA mutations (48 weeks, n=9) compared with singly mutated (20 weeks, n=31) or wild-type (7.5 weeks, n=6) tumors; however, this was not statistically significant[463]. A Phase 1a trial of single-agent alpelisib in advanced solid tumors reported an ORR of 6.0% (8/134) and a DCR of 58.2% (78/134), with objective responses observed for patients with breast, endometrial, cervical, and colorectal cancer (CRC); the DCR was 60.9% (14/23) in ER+/HER2– breast cancer, 68.4% (13/19) in head and neck cancer, 100% (5/5) in cervical cancer, and 34.3% (12/35) in CRC[143]. Combining alpelisib with the MEK inhibitor binimetinib in RAS- or BRAF-mutated advanced solid tumors elicited PRs for 75.0% (3/4) of patients with KRAS-mutated ovarian cancer, 1 PR for a patient with NRAS-mutated melanoma, and 1 unconfirmed PR for a patient with KRAS-mutated endometrial cancer[464].

Avelumab

Assay findings association

Tumor Mutational Burden
24 Muts/Mb

AREAS OF THERAPEUTIC USE

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 Merkel cell carcinoma, or for urothelial carcinoma in various treatment settings. The combination of avelumab and axitinib is FDA approved for patients with renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In a Phase 1b study evaluating single-agent avelumab for the treatment of patients with non-small cell lung cancer (NSCLC), the ORR was 12% (22/184) in previously treated patients and 18.7% (14/75) in the first-line setting, and the median PFS was 12 weeks for both cohorts[465-466]. In patients with NSCLC and PD-L1-positive tumor cells, first-line treatment with avelumab resulted in numerically increased ORR (20%; 7/35 vs. 0%; 0/10) and a trend toward prolonged PFS (11.6 vs. 6.0 weeks) relative to patients with fewer than 1% of tumor cells expressing PD-L1[465]; however, response rates, PFS, and OS were similar regardless of immune or tumor cell PD-L1 expression in patients who had previously received platinum-based treatment[466].

Cemiplimab

Assay findings association

Tumor Mutational Burden
24 Muts/Mb

AREAS OF THERAPEUTIC USE

Cemiplimab 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 to treat patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) that is not amenable to surgery or radiation therapy.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,37-45] , patients with NSCLC whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

A Phase 1 trial for patients with advanced NSCLC reported a 40% ORR (8/20; 1 CR and 7 PRs) and 60% DCR following treatment with cemiplimab monotherapy and an 18.2% ORR (6/33; 6 PRs) and 73% DCR for patients who received cemiplimab and radiotherapy[467].

Everolimus

Assay findings association

PIK3CA
E453K, M1043I

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; 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[132-133,136] and preclinical[137] evidence in multiple tumor types, PIK3CA activation may predict sensitivity to mTOR inhibitors such as everolimus.

SUPPORTING DATA

A trial of everolimus as a monotherapy in non-small cell lung cancer (NSCLC) showed modest activity[468], but a Phase 2 study of everolimus in combination with docetaxel did not show any added benefit of everolimus in an unselected population[469]. A Phase 1 study evaluated the addition of everolimus to carboplatin and paclitaxel +/- bevacizumab in advanced NSCLC and found the combinations produced 1 CR and 10 PRs (n=52), although treatments were not well tolerated[470]. A Phase 1 study in patients with advanced NSCLC of the combination of everolimus and erlotinib reported 9 objective responses and 28 patients experiencing SD (n=74), but a Phase 2 study found the combination inefficacious at tolerated doses[471-472] . A trial of combination treatment with sorafenib and everolimus reported 1 PR and 1 SD in 2 patients with lung adenocarcinoma, with both patients experiencing progression-free survival of more than 4 months[473]. 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[474], 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[475].

Temsirolimus

Assay findings association

PIK3CA
E453K, M1043I

AREAS OF THERAPEUTIC USE

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[134-135,476] and preclinical[137] 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%)[134] and 7/23 (30%)[476] were reported in patients with PIK3CA-mutant tumors.

SUPPORTING DATA

In a Phase 2 clinical trial in non-small cell lung cancer (NSCLC), front-line temsirolimus monotherapy demonstrated some clinical benefit but failed to meet the trial's primary end point[477]. In a Phase 1 trial of temsirolimus and radiation in patients with NSCLC, of 8 evaluable patients, 3 exhibited PR and 2 exhibited SD[478].

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

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CLINICAL TRIALS

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

BIOMARKER

Tumor Mutational Burden

RESULT

24 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 or anti-PD-L1 immune checkpoint inhibitors.

NCT02715284

PHASE 1

A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Patients With Advanced Solid Tumors

TARGETS
PD-1

LOCATIONS: Georgia, North Carolina, Florida, Alabama, Tennessee, Virginia, West Virginia, Ohio

NCT03257722

PHASE 1/2

Pembrolizumab + Idelalisib for Lung Cancer Study

TARGETS
PD-1, PI3K-delta

LOCATIONS: Georgia

NCT03833154

PHASE 3

Durvalumab vs Placebo Following Stereotactic Body Radiation Therapy in Early Stage Non-small Cell Lung Cancer Patients

TARGETS
PD-L1

LOCATIONS: Georgia, South Carolina, North Carolina, Alabama, Virginia, Florida, Ohio, West Virginia

NCT04026412

PHASE 3

A Study of Nivolumab and Ipilimumab in Untreated Patients With Stage 3 NSCLC That is Unable or Not Planned to be Removed by Surgery

TARGETS
PD-1, CTLA-4, PD-L1

LOCATIONS: South Carolina, Ohio, Florida, Maryland, Michigan, Texas, Rimouski (Canada), Colorado

NCT03829332

PHASE 3

Efficacy and Safety Study of Pembrolizumab (MK-3475) With or Without Lenvatinib (MK-7902/E7080) in Adults With Programmed Cell Death-Ligand 1 (PD-L1)-Positive Treatment-naïve Non-small Cell Lung Cancer (NSCLC)(MK-7902-007/E7080-G000-314/LEAP-007)

TARGETS
FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Georgia, North Carolina, Kentucky, Florida, Ohio, Maryland, Indiana, Windsor (Canada), Illinois, Missouri

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CLINICAL TRIALS

NCT03800134

PHASE 3

A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer

TARGETS
PD-L1

LOCATIONS: South Carolina, North Carolina, Florida, Kentucky, Maryland, New Jersey

NCT03369223

PHASE 1/2

An Investigational Immunotherapy Study of BMS-986249 Alone and in Combination With Nivolumab in Solid Cancers That Are Advanced or Have Spread

TARGETS
CTLA-4, PD-1

LOCATIONS: South Carolina, Ohio, Virginia, Maryland, Pennsylvania, Florida, New York, New Jersey, Texas

NCT02091141

PHASE 2

A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf/Cotellic, and Erivedge Treatment Targeted Against Certain Mutations in Cancer Patients

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

LOCATIONS: Georgia, North Carolina, Tennessee, Florida, Ohio

NCT02869789

PHASE 4

An Investigational Immuno-therapy Study for Safety of Nivolumab in Combination With Ipilimumab to Treat Advanced Cancers

TARGETS
CTLA-4, PD-1

LOCATIONS: Georgia, South Carolina, North Carolina, Tennessee, Florida, Alabama, Kentucky

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, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: North Carolina, Georgia, Alabama, Virginia, Indiana, Pennsylvania, Florida, Michigan

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GENE
ARID1A

ALTERATION
Q944*, Y471*

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

NCT02487095

PHASE 1/2

Trial of Topotecan With VX-970, an ATR Kinase Inhibitor, in Small Cell Cancers

TARGETS
ATR

LOCATIONS: Maryland

NCT02595931

PHASE 1

ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
ATR

LOCATIONS: North Carolina, Florida, Tennessee, Pennsylvania, Connecticut, Massachusetts, California

NCT02278250

PHASE 1

An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-803/M4344 as a Single Agent and in Combination With Cytotoxic Chemotherapy in Participants With Advanced Solid Tumors

TARGETS
ATR

LOCATIONS: Tennessee, Michigan, New Jersey, Wisconsin, Massachusetts, London (United Kingdom), Sutton (United Kingdom), Madrid (Spain), Rotterdam (Netherlands), Valencia (Spain)

NCT02723864

PHASE 1

Veliparib (ABT-888), an Oral PARP Inhibitor, and VX-970, an ATR Inhibitor, in Combination With Cisplatin in People With Refractory Solid Tumors

TARGETS
PARP, ATR

LOCATIONS: Maryland, Massachusetts, Texas

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, California, Withington (United Kingdom), Cambridge (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Saint Herblain (France), Villejuif (France), Seoul (Korea, Republic of)

NCT03641547

PHASE 1

M6620 Plus Standard Treatment in Oesophageal and Other Cancer

TARGETS
ATR

LOCATIONS: Glasgow (United Kingdom), Cardiff (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

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CLINICAL TRIALS

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT02630199

PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
ATR

LOCATIONS: Seoul (Korea, Republic of)

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GENE
EGFR

ALTERATION
A289V, L858R

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.

NCT03521154

PHASE 3

A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer (LAURA)

TARGETS
EGFR

LOCATIONS: Georgia, Maryland, Wisconsin, California, Sevilla (Spain), San Salvador de Jujuy (Argentina), Madrid (Spain), San Sebastián (Spain), Málaga (Spain), Valencia (Spain)

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, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: North Carolina, Georgia, Alabama, Virginia, Indiana, Pennsylvania, Florida, Michigan

NCT03381274

PHASE 1/2

Oleclumab (MEDI9447) EGFRm NSCLC Novel Combination Study

TARGETS
EGFR, ADORA2A, CD73

LOCATIONS: Georgia, Maryland, Illinois, New York, Connecticut, Texas, Colorado, California, Seoul (Korea, Republic of)

NCT03260491

PHASE 1

U3-1402 in Metastatic or Unresectable Non-Small Cell Lung Cancer

TARGETS
ERBB3

LOCATIONS: Georgia, Tennessee, New York, Massachusetts, California, Washington, Tokyo (Japan), Shizuoka (Japan), Osaka (Japan)

NCT02795156

PHASE 2

Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations

TARGETS
BRAF, KIT, PDGFRs, RET, VEGFRs, EGFR, ERBB2, ERBB4, MET, ROS1

LOCATIONS: Tennessee, Florida, Wisconsin, Missouri, Colorado

NCT02496663

PHASE 1

EGFR Inhibitor AZD9291 and Necitumumab in Treating Patients With EGFR-Positive Stage IV or Recurrent Non-small Cell Lung Cancer Who Have Progressed on a Previous EGFR Tyrosine Kinase Inhibitor

TARGETS
EGFR

LOCATIONS: Georgia, District of Columbia, Pennsylvania, Massachusetts, Colorado, California

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CLINICAL TRIALS

NCT04075396

PHASE 1/2

A Study of YH25448 in Participants With Epidermal Growth Factor Receptor (EGFR) Mutation Positive Advanced Non-Small Cell Lung Cancer (NSCLC)

TARGETS
EGFR

LOCATIONS: Tennessee, Florida, New York, California, Manchester (United Kingdom), Madrid (Spain), Malaga (Spain), Barcelona (Spain)

NCT03831932

PHASE 1/2

Glutaminase Inhibitor CB-839 Hydrochloride and Osimertinib in Treating Patients With EGFR-Mutated Stage IV Non-small Cell Lung Cancer

TARGETS
EGFR, GLS

LOCATIONS: Kentucky, Ohio

NCT02971501

PHASE 2

Osimertinib With or Without Bevacizumab in Treating Patients With EGFR Positive Non-small Cell Lung Cancer and Brain Metastases

TARGETS
VEGFA, EGFR

LOCATIONS: Florida, Ohio, Pennsylvania, Connecticut, Kansas, Nebraska, Utah, California

NCT03944772

PHASE 2

Phase 2 Platform Study in Patients With Advanced Non-Small Lung Cancer Who Progressed on First-Line Osimertinib Therapy (ORCHARD)

TARGETS
EGFR, MET, PD-L1

LOCATIONS: Maryland, New York, Connecticut, Massachusetts, Texas, California, Washington, A Coruña (Spain)

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GENE
PIK3CA

ALTERATION
E453K, M1043I

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: North Carolina, Georgia, Kentucky

NCT02761694

PHASE 1

Phase 1 Study of ARQ 751 in Solid Tumors With AKT1, 2, 3 Genetic Alterations, Activating PI3K Mutations or PTEN-null

TARGETS
AKTs

LOCATIONS: South Carolina, Tennessee, Texas, Oklahoma

NCT01827384

PHASE 2

Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, mTOR, MEK, WEE1

LOCATIONS: Kentucky, Maryland, Pennsylvania, New Jersey, Texas, Colorado

NCT03735628

PHASE 1/2

An Study to Evaluate the Safety and Efficacy of Copanlisib in Combination With Nivolumab in Patients With Advanced Solid Tumors

TARGETS
PI3K, PD-1

LOCATIONS: Ohio, New York, Toronto (Canada), Rhode Island, California

NCT03006172

PHASE 1

To Evaluate the Safety, Tolerability, and Pharmacokinetics of GDC-0077 Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer

TARGETS
PI3K-alpha, Aromatase, CDK4, CDK6, ER

LOCATIONS: Tennessee, New York, Toronto (Canada), Massachusetts, London (United Kingdom), Surrey (United Kingdom), Bordeaux (France), Villejuif (France), Valencia (Spain), Barcelona (Spain)

NCT03502733

PHASE 1

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

TARGETS
PI3K, PD-1

LOCATIONS: Maryland, Texas

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CLINICAL TRIALS

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

NCT01920061

PHASE 1

A Study Of PF-05212384 In Combination With Other Anti-Tumor Agents

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, EGFR, ERBB2, ERBB4

LOCATIONS: Alabama

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

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NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ALOX12B
E176K

ARID1A
S446C

BRD4
M1152I

CDK12
R202L

LTK
L364V

LYN
E110Q

MAP3K1
Q280H

NBN
D469N

NT5C2
S213F

PALB2
E830Q

PIK3C2B
V729M

PIK3C2G
D870N

SPEN
D1372H, E1608K, E1682K, R1229S and R1241Q

TEK
loss

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. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

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

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

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

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

The median exon coverage for this sample is 987x

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TEST PRINCIPLE

FoundationOne®CDx (F1CDx) is performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The assay employs 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 (refer to Table 2 and Table 3 for complete list of genes included in F1CDx). In total, the assay detects alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid capture–selected libraries are sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data is then processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous gene deletions), and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and positive homologous recombination deficiency (HRD) status (tBRCA-positive and/or LOH high) are 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. A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
4. Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*.
5. 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.
6. 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.
7. The MSI-H/MSS designation by FMI FoundationOne®CDx (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 https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf 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. Patients with microsatellite status of "Cannot Be Determined" should be retested with an orthogonal (alternative) method. The clinical validity of the qualitative MSI designation has not been established.
8. TMB by F1CDx is defined based by 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. TMB is a function of the characteristics of a patient's specimen and testing parameters; therefore, TMB may differ among specimens (e.g., primary vs. metastatic, tumor content) and targeted panels. 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 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 not been established.
9. 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.
10. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.
11. Alterations in polyT homopolymer runs may not be reliably detected in BRCA1/2.
12. Certain large rearrangements in BRCA1/2 including large scale genomic deletions (affecting at least one whole exon), insertions or other deleterious genomic rearrangements

including inversions or transversion events, may not be detected in an estimated 5% of ovarian cancer patients with BRCA1/2 mutations by F1CDx.

13. Certain potentially deleterious missense or small in-frame deletions in BRCA1/2 may not be reported under the "CDx associated findings" but may be reported in the "Other alterations and biomarkers identified" section in the patient report.
14. Alterations at allele frequencies below the established limit of detection may not be detected consistently.
15. Detection of LOH has been verified only for ovarian cancer patients.
16. Performance of the LOH classification has not been established for samples below 35% tumor content and with LOH scores near the cutoff of 16.
17. 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.

PDF Service Version 2.9.0

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)

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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 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.

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.

LOSS OF HETEROZYGOSITY SCORE

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. 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.

MICROSATELLITE STATUS

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

TUMOR MUTATIONAL BURDEN

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations 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 is reported in Professional Services as the number of mutations per megabase (Muts/Mb) rounded to the nearest integer. 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.

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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

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