SUMMIT PATHOLOGY
Offices located at Poudre Valley Hospital
1024 South Lemay Avenue
Fort Collins, CO 80524
Tel: (970) 495-8740
Fax: (970) 495-7605

ABNORMAL

NON-GYN CYTOPATHOLOGY REPORT

ADDENDED

Patient: GATTON, ROSE M
Med Rec#: **2655125** PV: **177254556**
DOB: **10/04/1962** Age: **57** Sex: **F**
Physician(s):
DEPRIEST KIRK D.O. POUDRE VALLEY HOSPITAL

Accession #: 12115595
Date Collected: **06/17/2020**
Date Received: **06/17/2020**
Date Reported: **06/19/2020**
Report Modified: **07/14/2020**

Test Requested: **PVH Non-Gyn Cytology**
Result ID: VC20-00407

Revision (07/14/2020)

ADDENDUM:

This case is being addended to refer the reader to the detailed Foundation One CDx Medicine report.

Block A1 was used for this study.

Note: Please see full report for details. Report is attached. ly

Heath D Worcester, MD
Pathologist, Electronic Signature

FINAL DIAGNOSIS:

LUNG, RIGHT LOWER LOBE, ENDOBRONCHIAL ULTRASOUND-GUIDED FNA:
1. ADEQUATE FOR EVALUATION
2. MALIGNANT
3. COMPATIBLE WITH POORLY-DIFFERENTIATED NON-SMALL CELL CARCINOMA

COMMENT:

This patient has a reported history of lung cancer which is not in our files/LIS. No definitive glandular or squamous differentiation is present. The findings, given the IHC expression, may present a poorly-differentiated squamous carcinoma, adenocarcinoma or adenosquamous carcinoma. That said, an adenocarcinoma is favored given rare NapsinA positivity and negative p40 expression.

Heath D Worcester, MD
Pathologist, Electronic Signature

The case has been reviewed with the following pathologists who concur with the interpretation: Michael Walts, MD

Clinical History: Lung cancer recurrence. Right lower lobe mass.

GROSS DESCRIPTION:

RLL MASS: Received in CytoLyt, labeled with the patient's name and "A. RLL Biopsy", are 28 mL of pale pink, hazy fluid.

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Routine ThinPrep is performed. Sample is dilute.

Received in Formalin, labeled with the patients name and "A. RLL Lung FNA", are 26 mL of dark red, opaque fluid. One cell block is prepared using buffered 10% formalin.

Also received labeled with the patient's name, are 3 Diff-Quik stained slides and 3 fixed slides.

INTRAOPERATIVE CONSULT DIAGNOSIS:

FNA Adequacy: A. lesional request additional tissue for cell block (10:48 hrs)
6/17/20 [performed by Jeremiah Andersen, MD]

MICROSCOPIC DESCRIPTION:

1 Thin prep, 6 direct smears and 1 cell block examined.
Also examined are immunoperoxidase-stained sections for pankeratin, panmelanoma, CK5/6, CK7, CK20, TTF-1, NapsinA, CDX-2, and p40 which show tumor positivity with pankeratin, CK5/6, CK7, and rare NapsinA positivity in the tumor. The remaining stains are negative in the tumor cells (Positive and negative controls appropriate).

(Note: The immunoperoxidase tests utilized in this examination were developed and their performance characteristics determined by the laboratory at Summit Pathology. They have not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. These tests are used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing.)

CPT Code(s): 88341 x8, 88172, G9418, 88173, 88305, 88342

Specimen processed and screened at: Summit Pathology, 5802 Wright Dr, Loveland, CO 80538
Specimen interpreted at: Poudre Valley Hosp 1024 S Lemay, Fort Collins, CO 80524

FOUNDATIONONE®CDx

PATIENT
Gatton, Rose

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE
13 Jul 2020

ORDERED TEST #
ORD-0841921-01

PATIENT

DISEASE Lung non-small cell lung carcinoma (NOS)
NAME Gatton, Rose
DATE OF BIRTH 04 October 1962
SEX Female
MEDICAL RECORD # 2655125

PHYSICIAN

ORDERING PHYSICIAN Kemme, Douglas
MEDICAL FACILITY University of Colorado Health - Greeley
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 204658
PATHOLOGIST Worcester, Heath

SPECIMEN

SPECIMEN SITE Lung
SPECIMEN ID VC20-00407-A1
SPECIMEN TYPE Block
DATE OF COLLECTION 17 June 2020
SPECIMEN RECEIVED 01 July 2020

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
Tumor Mutational Burden (TMB) ≥ 10 Muts/Mb	Keytruda® (Pembrolizumab)

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported. See Appendix: About FoundationOne CDx for details.

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 Cannot Be Determined § *
Tumor Mutational Burden 11 Muts/Mb §
CCND1 amplification §
FGF19 amplification §
FGF3 amplification §
FGF4 amplification §
KRAS G12F
STK11 I192fs*95
TP53 G245V

**Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.*

§ 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).

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

Electronically signed by Julie Tse, M.D. | 13 July 2020
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

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)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	Tabrecta™ (Capmatinib)
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)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre™ (Pemigatinib)
Prostate Cancer	Homologous Recombination Repair (*HRR*) gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*) alterations	Lynparza® (Olaparib)
Solid Tumors	*TMB* ≥ 10 mutations per megabase	Keytruda® (Pembrolizumab)

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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.

PATIENT

DISEASE Lung non-small cell lung carcinoma (NOS)
NAME Gatton, Rose
DATE OF BIRTH 04 October 1962
SEX Female
MEDICAL RECORD # 2655125

PHYSICIAN

ORDERING PHYSICIAN Kemme, Douglas
MEDICAL FACILITY University of Colorado Health - Greeley
ADDITIONAL RECIPIENT None
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PATHOLOGIST Worcester, Heath

SPECIMEN

SPECIMEN SITE Lung
SPECIMEN ID VC20-00407-A1
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Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported.

Biomarker Findings

Tumor Mutational Burden - 11 Muts/Mb
Microsatellite status - Cannot Be Determined

Genomic Findings

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

CCND1 amplification - equivocal†
STK11 I192fs*95
KRAS G12F
FGF19 amplification - equivocal†
FGF3 amplification - equivocal†
FGF4 amplification - equivocal†
TP53 G245V

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

† See About the Test in appendix for details.

11 Therapies with Clinical Benefit
0 Therapies with Lack of Response
38 Clinical Trials

BIOMARKER FINDINGS

Tumor Mutational Burden - 11 Muts/Mb

10 Trials *see p. 17*

Microsatellite status - Cannot Be Determined

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

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
CCND1 **-** amplification - equivocal	none	Abemaciclib
		Palbociclib
10 Trials *see p. 19*		Ribociclib
STK11 **-** I192fs*95	none	Everolimus
10 Trials *see p. 23*		Temsirolimus
KRAS **-** G12F	none	none
10 Trials *see p. 21*		

☐ *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
11 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 mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[29-30] and cigarette smoke in lung cancer[5,31], treatment with temozolomide-based chemotherapy in glioma[32-33], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[34-38], and microsatellite instability (MSI)[34,37-38]. 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[1-2,5-15,19,39-47].

BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

On the basis of prospective clinical evidence in multiple solid tumor types, MSI and associated increased mutational burden[48-49] may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors[49-53], including the approved therapies nivolumab[54-55], pembrolizumab[5,56], atezolizumab, avelumab, and durvalumab[50-52] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[57-62], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[63-66]. 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[57].

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[67].

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[67-69]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered. While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[67], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[70]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[70-72] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[73-75]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

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GENE
CCND1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[76-80], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[79,81]. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial[82]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[82]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[83].

FREQUENCY & PROGNOSIS
CCND1 amplification has been reported in 2-25% of lung adenocarcinoma[24,84-86] and 6-38% of lung squamous cell carcinoma[84-85,87] cases. Expression of cyclin D1 has been reported in 59% (36/61) of non-small cell lung cancer (NSCLC) tumors analyzed[88]. The prognostic significance of CCND1 amplification in NSCLC is not clear[89]. Cyclin D1 protein expression was not associated with clinicopathologic parameters of NSCLC in one study[88].

FINDING SUMMARY
CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression[90] and may lead to excessive proliferation[91-92].

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GENE
STK11

ALTERATION
I192fs*95

TRANSCRIPT NUMBER
NM_000455

CODING SEQUENCE EFFECT
574delA

POTENTIAL TREATMENT STRATEGIES

STK11 alteration is associated with poorer response to immune checkpoint inhibitors for patients with non-small cell lung cancer (NSCLC), including those with tumors harboring co-occurring KRAS or KEAP1 mutations. Following anti-PD-1-based regimens, retrospective analyses have reported shorter OS for patients with KRAS and STK11 co-mutated tumors than for patients with wild-type STK11 (6.4 vs. 16.1 months, HR=1.99)[93], as well as markedly fewer objective responses for patients with KRAS/STK11 co-mutated versus KRAS/TP53 co-mutated tumors in the CheckMate-057 (0% [0/6] vs. 57% [4/7])[93] and GEMINI (0% [0/6] vs. 53% [9/17])[94] trials. Similar objective responses were observed for patients receiving combination anti-PD-1 and anti-CTLA-4 treatment in CheckMate-012 (0% [0/3] KRAS/STK11 vs. 78% [7/9] KRAS/TP53)[11], although a case study reported ongoing response for 1 patient with KRAS/STK11 co-mutations treated with nivolumab and ipilimumab[95]. Patients with NSCLC and concurrent mutation of STK11 and KEAP1 (n=39) who received treatment with a PD-L1 inhibitor experienced significantly shorter PFS (1.6 vs. 2.5 months; HR=1.5) and OS (4 vs. 11 months; HR=1.9) compared with patients with STK11- and KEAP1-wild-type tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 Muts/Mb)[96]. Lower ORR (31.3% vs. 60.6%) and shorter median PFS (6.4 vs. 11 months) and OS (9.8 vs. 22.4 months) have also been reported for patients with NSCLC harboring STK11/LKB1 mutations compared with wild-type STK11/LKB1[97]. However, an exploratory analysis of a subset of patients with PD-L1-positive NSCLC treated in the first-line setting with pembrolizumab showed improved ORR and OS irrespective of STK11 or KEAP1 mutation status[98]. In multiple Phase 1 and Phase 2 trials, durvalumab-based treatments were associated with lower ORRs for patients with STK11-mutated versus STK11-wild-type NSCLC (0–6% vs. 16–25%)[99]. STK11 mutation is an independent predictor of shorter treatment duration on nivolumab for patients with NSCLC[100] and correlates with reduced PD-L1 expression[101-104] and T-cell infiltration[103-107]. Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations[108-112]. A PJS patient with pancreatic cancer and an STK11 mutation experienced a partial response to the mTOR inhibitor everolimus[113]. In one preclinical study, STK11 loss was associated with sensitivity to combination treatment including a SRC inhibitor[114]; however, the clinical relevance of these findings has not been established.

FREQUENCY & PROGNOSIS

Several clinical studies have found STK11 mutation to be common in non-small cell lung cancer (NSCLC) (15-35%), with alterations more prevalent in lung adenocarcinomas (13-34%) than in lung squamous cell carcinoma (2-19%)[24,87,109,115-118]. In the TCGA datasets, STK11 homozygous deletion was observed in 1% of lung adenocarcinoma cases[86] and was not observed in any of 178 lung squamous cell carcinoma cases[87]. STK11 mutations in NSCLC often co-occur with activating KRAS mutations[117-118]. In transgenic mouse models, animals expressing mutant KRAS developed lung adenocarcinomas, whereas the KRAS-mutant/LKB1-deficient mice developed an expanded histological spectrum of tumors that included large cell and squamous cell carcinomas[109]. Strongly decreased or absent expression of LKB1 correlated with inferior outcome in patients with NSCLC treated with bevacizumab-containing chemotherapy; expression of LKB1 was not prognostic in patients treated with chemotherapy without bevacizumab[119].

FINDING SUMMARY

The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels[108]. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis[114,120]. Functional disruption of the STK11 kinase domain (amino acids 49-309) or STRAD binding domain (amino acids 320-343) through mutation or loss, such as observed here, is predicted to be inactivating[121-132]. Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation[133]. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly[133-135]. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers[133-135], and individuals with this syndrome have a 30-50% risk of developing breast cancer[133,135]. Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.

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GENE
KRAS

ALTERATION
G12F

TRANSCRIPT NUMBER
NM_004985

CODING SEQUENCE EFFECT
34_35GG>TT

POTENTIAL TREATMENT STRATEGIES

Combination of a RAF-MEK inhibitor CH5126766 and FAK inhibitor defactinib elicited clinical responses for patients with low grade serous ovarian cancer (PR rate 50% [4/8]) and non-small cell lung cancer (PR rate 10% [1/10]) with KRAS mutations[136]. Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib and cobimetinib[137-142]. Multiple clinical studies have reported either low response rates or response rates similar to those of chemotherapy in patients with KRAS-mutated NSCLC receiving MEK inhibitors as a monotherapy[143-145]. In a Phase 3 study, the addition of selumetinib to docetaxel did not significantly improve the PFS or OS of patients with KRAS-mutant NSCLC relative to docetaxel alone[146]. In a Phase 1/1b study evaluating trametinib with either docetaxel or pemetrexed, responses were independent of KRAS mutation status[147]. Combinatorial approaches involving MEK inhibitors and other targeted therapies, including PI3K or EGFR inhibitors, have generally had limited clinical efficacy in patients with NSCLC and have been associated with high toxicity[148-150] despite preclinical evidence supporting the effectiveness of combinatorial strategies involving inhibitors of PI3K[151-152], RAF[153], pan-ERBB[154], or BCL2[155-156]. However, a Phase 1 combination trial of the MEK inhibitor PD-0325901 with the CDK4/6 inhibitor palbociclib that included 17 patients with KRAS-mutant NSCLC reported 1 PR, >50% SD, and 5 patients with PFS >6 months; clinical benefit was seen among patients with tumors harboring KRAS mutation alone or together with inactivation of TP53 or CDKN2A/B, but not among patients with tumors harboring KRAS mutation and STK11 inactivation[157]. The CDK4/6 inhibitor abemaciclib demonstrated increased activity in KRAS-mutated NSCLC compared to KRAS-wildtype NSCLC (median PFS of 2.8 vs. 1.9 months) in a Phase 1 trial[79] but did not prolong median OS compared to erlotinib (7.4 vs. 7.8 months, HR=0.97), in spite of improved PFS (3.6 vs. 1.9 months, HR=0.58) and ORR (8.9% vs. 2.7%) relative to erlotinib, in a Phase 3 study for patients with platinum-refractory KRAS-mutated advanced NSCLC[158]. Although some studies have suggested that KRAS mutation status may predict a lack of response to the EGFR inhibitors erlotinib and gefitinib in patients with lung cancer, a retrospective study suggests that there is no statistically significant difference in response to EGFR tyrosine kinase inhibitors among KRAS-wildtype and KRAS-mutated patients[159-162]. A study assessing the immune checkpoint inhibitor nivolumab for pretreated patients with KRAS-mutated (n=206) or KRAS-wildtype (n=324) advanced NSCLC observed a similar ORR (20% vs. 17%), median PFS (4 vs. 3 months) and OS (11.2 vs. 10 months) in both cohorts, although the 3-month PFS rate was significantly longer in KRAS-positive than KRAS-negative patients (53% vs. 42%)[163]. Co-occurring KRAS and STK11 alterations are associated with poorer response to immune checkpoint inhibitors for patients with NSCLC. Following anti-PD-1-based regimens, retrospective analyses have reported shorter OS for patients with KRAS- and STK11-mutated tumors than for those whose KRAS-mutated tumors were STK11-wildtype (6.4 vs. 16.1 months, HR=1.99), as well as markedly fewer objective responses for patients with KRAS-/STK11-mutated versus KRAS-/TP53-mutated tumors in the CheckMate-057 (0% [0/6] vs. 57% [4/7])[93] and GEMINI (0% [0/6], vs. 53% [9/17])[164]. Another study observed that patients with NSCLC and KRAS-mutated tumors without STK11 alteration who were treated with second-line immunotherapy experienced similar median PFS (2.8 vs. 2.2 months, HR = 1.64) and numerically longer median OS (7.7 vs. 3.5 months, HR = 2.3; p=0.09) compared to patients harboring mutations in both KRAS and STK11[165]. The reovirus Reolysin targets cells with activated RAS signaling[166-168] 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[169-177]. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear[178].

FREQUENCY & PROGNOSIS

Studies have reported KRAS mutations in 10-38% of non-small cell lung cancers (NSCLC), including 27-37% of lung adenocarcinomas[23-24,86,179-187], 10.5-33% of lung adenosquamous carcinomas[188-190], 22% of lung large cell carcinoma without neuroendocrine features, and 6% of lung large cell neuroendocrine carcinomas[191]. KRAS mutation was associated with shorter PFS (7.0 vs. 8.6 months, p=0.026) and OS (14.2 vs. 21.6 months, p=0.019) with first-line treatment with bevacizumab plus chemotherapy in a retrospective study[192] and a lower major pathological response rate (0% [0/10] vs. 35.5% [11/31]) after neoadjuvant bevacizumab plus chemotherapy followed by adjuvant bevacizumab in a Phase 2 trial[193], relative to those patients lacking KRAS mutation. However, addition of atezolizumab to first-line bevacizumab and chemotherapy improved PFS regardless of KRAS status in the Phase 3 IMpower150 study (HR=0.50 for KRAS mutant vs. 0.47 for KRAS wild-type vs. 0.67 for KRAS unknown)[194]. In one study of 55 patients with lung adenocarcinoma, KRAS mutations, especially in combination with TP53 alterations, correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab, likely as a consequence of association with some immunogenic features such as tumor mutation burden[104]. KRAS mutation in lung adenocarcinoma has been correlated with disease progression, poorly differentiated tumors, and aggressive tumor behavior[181,187,195]. However, the prognostic value of KRAS mutation in lung adenocarcinoma may differ among ethnic groups and may depend upon the specific allelic variant present[196].

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[138,197]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, and K117N have been characterized as activating and oncogenic[138,198-219].

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GENE
FGF19

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies that directly address genomic alterations in FGF19. However, FGF19 amplification predicts sensitivity to FGFR4 inhibitors in liver cancer cell lines[220-221]; selective FGFR4 inhibition reduced tumor burden in an FGF19-amplified HCC xenograft model[222]. A Phase 1 study of the FGFR4 inhibitor fisogatinib (BLU-554) for patients with previously treated hepatocellular carcinoma (HCC), most of whom had received prior sorafenib treatment, reported a 16.7% ORR (11/66, 1 CR, ongoing for >1.5 years) and a median PFS of 3.3 months for FGF19-IHC-positive patients; poorer outcomes (0% ORR, PFS of 2.3 months) were observed for patients with negative or unknown FGF19 IHC scores[223]. Acquisition of FGFR4 mutations may represent a mechanism of resistance for patients with FGF19 overexpression who initially responded but then progressed on fisogatinib[221]. Preliminary results from the dose escalation part of a Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, showed an ORR of 7.6% (4/53), SD rate of 52.8% (28/53), and a median time to progression of 4.1 months; responses were observed in both FGF19-positive and FGF19-negative cases[224]. In a retrospective analysis, a trend toward response to sorafenib treatment and FGF19 copy number gain was observed in patients with HCC, and 2 patients harboring FGF19 copy number gain experienced a CR[225]. A case study reported activity of pan-FGFR inhibitors in FGF-amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[226]. Other therapies targeting FGF19 or FGFR4 signaling are in development[227].

FREQUENCY & PROGNOSIS

In the TCGA datasets, FGF19 amplification has been reported with highest incidence in esophageal carcinoma (34%), head and neck squamous cell carcinoma (23%), breast carcinoma (14%), lung squamous cell carcinoma (13%), and bladder urothelial carcinoma (10%) (cBioPortal, 2020). In HCC, FGF19 is an important driver gene[222,228-229], and FGF19 protein expression correlates with tumor progression and poorer prognosis[230]. Exogenous FGF19 has been shown to promote prostate cancer tumorigenesis in a preclinical study[231], and the presence of FGF19-positive tissues is an independent factor for worse prognosis following radical prostatectomy[232].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[222,233]. FGF19 lies in a region of chromosome 11q13 frequently amplified in a diverse range of malignancies that also contains FGF3, FGF4, and CCND1[234]. Correlation between FGF19 amplification and protein expression has been demonstrated in hepatocellular carcinoma (HCC)[235] but was not observed in several other tumor types[229].

GENE
FGF3

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[236].

FREQUENCY & PROGNOSIS

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[91].

FINDING SUMMARY

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures[237].

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GENE
FGF4

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies[238-239] and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)[238]. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[236].

FREQUENCY & PROGNOSIS

FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[91] including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 23%), breast invasive carcinoma (14%), lung squamous cell carcinoma (13%), bladder urothelial carcinoma (10%), ovarian serous cystadenocarcinoma (5%), stomach adenocarcinoma (7%), skin melanoma (4%), and hepatocellular carcinoma (HCC; 5%), however FGF4 amplification is rare in hematopoietic and lymphoid malignancies, reported in less than 1% of samples analyzed (cBioPortal, 2020).

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[240] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[241]. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers[91,238,242-245] and may confer sensitivity to the multi-kinase inhibitor sorafenib[238].

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GENE
TP53

ALTERATION
G245V

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
734G>T

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[246-249], or p53 gene therapy and immunotherapeutics such as SGT-53[250-254] and ALT-801[255]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[256]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[257]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[258]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[259]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[260]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[261]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[254]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[262]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[263-265]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[266]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[267-268]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[269-270]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[86-87,271-276], including 38-54% of lung adenocarcinomas and 47-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Sep 2019)[24-25,86-87]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[104]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[277].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[278]. Alterations that have been functionally characterized as inactivating and/or result in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, are thought to dysregulate the transactivation of p53-dependent genes and are predicted to promote tumorigenesis[279-283]. One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with Li-Fraumeni syndrome (ClinVar, Mar 2020)[284]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[285-287], including sarcomas[288-289]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[290] to 1:20,000[289]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[291]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Atezolizumab

Assay findings association

Tumor Mutational Burden
11 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 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, triple-negative breast cancer, and hepatocellular carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,39-47] , 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 Phase 3 IMpower131 study, addition of atezolizumab to first-line carboplatin and paclitaxel improved median PFS for patients with squamous NSCLC compared with chemotherapy alone (6.3 vs. 5.6 months, HR=0.71); longer PFS was observed across PD-L1 expression subgroups[292]. 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[194,293-294] . 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[293]. 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[194]. 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[294]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic NSCLC reported improved median OS (20.2 vs. 13.1 months; HR=0.60), median PFS (8.1 vs. 5.0 months), and ORR (38.3% vs. 28.6%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[295]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in median OS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[296], confirming previous Phase 2 trial data[297-298] . Clinical benefit was observed for patients regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was achieved with tumor PD-L1 expression >50% (HR=0.41) compared with <1% (HR=0.75)[296]. 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[299].

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Durvalumab

Assay findings association

Tumor Mutational Burden
11 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[1-2,5-15,19,39-47] , 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 Phase 3 PACIFIC trial for patients with Stage 3 unresectable NSCLC who did not have progression on chemoradiotherapy (CT), durvalumab monotherapy improved PFS versus placebo across PD-L1 expression subgroups; PFS was 17.8 versus 5.6 months (HR=.46) for patients with PD-L1 expression ≥1%, and 10.7 versus 5.6 months (HR=.73) for patients with PD-L1 expression <1%. OS benefit was observed for patients with PD-L1 expression ≥1% (not reached [NR] vs. 29.6 months, HR=0.59), but not for those with PD-L1 expression <1% (33.1 vs. 45.6 months, HR=1.14)[300]. In the Phase 3 ARCTIC study for patients with metastatic NSCLC who had progressed on 2 or fewer prior therapies, single-agent durvalumab improved OS (11.7 vs. 6.8 months, HR=0.63) and PFS (3.8 vs. 2.2 months, HR=0.71) versus investigator's choice of standard of care (SOC) for patients in cohort A (PD-L1 ≥25%)[301]. However, durvalumab plus tremelimumab did not significantly improve OS (11.5 vs. 8.7 months, HR=0.80) or PFS (3.5 vs. 3.5 months, HR=0.77) compared with SOC for patients in cohort B (PD-L1 <25%)[301]. In the Phase 3 MYSTIC trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC and PD-L1 expression ≥25%, neither durvalumab monotherapy nor durvalumab plus tremelimumab improved OS versus chemotherapy (HR=0.76 and 0.85, respectively); however, patients with bTMB ≥20 Muts/Mb showed improved OS for durvalumab plus tremelimumab versus chemotherapy (21.9 vs. 10.0 months, HR=0.49)[302]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[303-304] and OS[303] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90%) had an ORR of 30.9% (21/68), compared with ORRs of 16.4% (24/146) for patients with ≥25% and 7.5% (7/93) for patients with <25% PD-L1 positivity, respectively[304]. Re-treatment with durvalumab for patients with PD-L1-positive (≥25%) EGFR- or ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or SD for 25.0% (10/40) of patients[305].

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Nivolumab

Assay findings association

Tumor Mutational Burden
11 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), metastatic small cell lung cancer (SCLC), and esophageal squamous cell carcinoma (ESCC). 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[1-2,5-15,19,39-47] , 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)[306]. 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[307-308] . 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)[309]. 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)[310], despite Phase 1 results in the same setting suggesting improved ORR and OS[311].

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Pembrolizumab

Assay findings association

Tumor Mutational Burden
11 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 tumor mutational burden-high (TMB-H; ≥10 Muts/Mb), microsatellite instability-high (MSI-H), or mismatch-repair-deficient (dMMR) solid tumors, 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, Merkel cell carcinoma, or cutaneous squamous cell carcinoma (CSCC). 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[1-2,5-15,19,39-47] , 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

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)[312] and ≥50% (20.0–30.0 vs. 12.2–14.2 months, HR=0.63-0.69)[312-313] . 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[314]. 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)[315]. 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)[316] or squamous (KEYNOTE-407)[317-318] 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)[319]. 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[320]. 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[321-323] . Clinical activity has also been achieved with pembrolizumab in combination with ipilimumab[324], the HDAC inhibitor vorinostat[325], and the multikinase inhibitor lenvatinib[326].

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Abemaciclib

Assay findings association

CCND1
amplification - equivocal

AREAS OF THERAPEUTIC USE

Abemaciclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor-positive (HR+), HER2-negative (HER2–) advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women, in combination with fulvestrant for women who have progressed on endocrine therapy, or as monotherapy for adults who have progressed on endocrine therapy and chemotherapy in the metastatic setting. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in breast cancer and mantle cell lymphoma[79,327], CCND1 amplification or activation may be associated with response to abemaciclib. In a Phase 1 study, 4/10 patients with CCND1-amplified breast cancer responded to single-agent abemaciclib, with all of the responders having HR+ tumors[79].

SUPPORTING DATA

Abemaciclib monotherapy has been evaluated as second-line treatment for advanced non-small cell lung cancer (NSCLC), with specific focus on KRAS-mutated NSCLC based on preclinical and early clinical data[79,328] . In a Phase 3 trial for patients with platinum-refractory KRAS-mutated advanced NSCLC, however, abemaciclib did not prolong median OS (7.4 vs. 7.8 months, HR=0.97) compared to erlotinib[158]. Median PFS (3.6 vs. 1.9 months, HR=0.58) and ORR (8.9% vs. 2.7%) increased with abemaciclib, and no association of abemaciclib activity with KRAS co-mutations in STK11 or TP53 were observed[158]. As second-line therapy for squamous NSCLC, abemaciclib did not improve outcomes compared to docetaxel (median PFS of 2.5 vs. 4.2 months, ORR of 2.8% vs. 20.8%, and median OS of 7.0 vs. 12.4 months)[329]. A Phase 1b study in previously treated advanced NSCLC combined abemaciclib with pemetrexed, ramucirumab, or gemcitabine and reported a median PFS of 5.6 months, 4.8 months, and 1.6 months, respectively; the ORRs were 4.3% (1/23), 4.2% (1/24), and 5.1% (2/39), respectively[330].

Avelumab

Assay findings association

Tumor Mutational Burden
11 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[1-2,5-15,19,39-47] , 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[331-332]. 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[331]; 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[332].

Cemiplimab

Assay findings association

Tumor Mutational Burden
11 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. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-2,5-15,19,39-47] , 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[333].

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Everolimus

Assay findings association

STK11
I192fs*95

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. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Increased mTOR signaling is present in LKB1-deficient tumors[108-110,112,334] ; therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations[108]. Everolimus elicited clinical responses lasting >6 months in 2 patients with pancreatic cancer[113,335] and 1 patient with atypical pituitary adenoma[336], all of whom harbored STK11 alterations in their tumors.

SUPPORTING DATA

A trial of everolimus as a monotherapy in non-small cell lung cancer (NSCLC) showed modest activity[337], but a Phase 2 study of everolimus in combination with docetaxel did not show any added benefit of everolimus in an unselected population[338]. 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[339]. 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[340-341] . 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[342]. 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[150], 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[343].

Palbociclib

Assay findings association

CCND1
amplification - equivocal

AREAS OF THERAPEUTIC USE

Palbociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor (HR)-positive/HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as first-line therapy for postmenopausal women or in combination with fulvestrant following progression on endocrine therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical studies in liposarcoma and mantle cell lymphoma as well as responses in patients with breast cancer or melanoma indicate that activation of cyclin D-CDK4/6 may predict sensitivity to therapies such as palbociclib[80,83,344-345] .

SUPPORTING DATA

Palbociclib has been studied primarily for the treatment of ER+ breast cancer[77,346-347] . A Phase 2 study of palbociclib in patients with recurrent or metastatic non-small cell lung cancer (NSCLC) and loss of p16INK4a reported no responses in any of the 16 evaluable patients but stable disease (SD) in 8 (50%) patients[348]. A trial of the CDK4/6 inhibitor abemaciclib in patients with NSCLC reported a disease control rate of 51% (37% for patients with KRAS wild-type tumors and 54% for patients with KRAS-mutant tumors), with one confirmed PR[349].

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Ribociclib

Assay findings association

CCND1
amplification - equivocal

AREAS OF THERAPEUTIC USE

Ribociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved in combination with an aromatase inhibitor as first-line therapy to treat women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced or metastatic breast cancer. Ribociclib is also approved in combination with fulvestrant to treat postmenopausal women with HR+, HER2– advanced or metastatic breast cancer, either as first-line therapy or following disease progression on endocrine therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical responses for 3 patients with bladder cancer, BRAF/NRAS-wild-type melanoma, or ER-positive breast cancer[78,83], CCND1 amplification or expression may predict sensitivity to CDK4/6 inhibitors such as ribociclib. In a prospective trial, 1 out of 12 patients with CCND1-amplified solid tumors responded to ribociclib[83].

SUPPORTING DATA

A Phase 1b study evaluating ceritinib in combination with ribociclib for the treatment of patients with ALK+ NSCLC reported complete or partial response for 50% (4/8) of patients not previously treated with an ALK inhibitor, 64% (9/14) of patients with prior crizotinib treatment, and 0% (0/5) of patients with prior 3rd-generation ALK inhibitor treatment[350]. The Phase 1 Signature study of ribociclib for the treatment of patients with CDK4/6 pathway activated tumors reported clinical benefit for 18.4% (19/103) of cases, 58% (11/19) of whom had p16INK4a mutation or loss[83]. Phase 1 studies of ribociclib for the treatment of patients with Rb+ advanced solid tumors reported 2.4% partial responses and 23.5-34.4% stable diseases (SD)[78,351]; the 3 responders had alterations in the CDK4/6 pathway[78].

Temsirolimus

Assay findings association

STK11
I192fs*95

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Increased mTOR signaling is present in LKB1-deficient tumors[108-110,112,334] ; therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations[108].

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[352]. In a Phase 1 trial of temsirolimus and radiation in patients with NSCLC, of 8 evaluable patients, 3 exhibited PR and 2 exhibited SD[353].

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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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

11 Muts/Mb

RATIONALE

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

NCT03793179

PHASE 3

Firstline Pembrolizumab Alone or in Combination With Pemetrexed and Carboplatin in Induction/Maintenance or Postprogression in Treating Patients With Stage IV Non-squamous Non-small Cell Lung Cancer

TARGETS
PD-1

LOCATIONS: Colorado

NCT03456063

PHASE 3

A Study of Neoadjuvant Atezolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in Patients With Resectable Stage II, IIIA, or Select IIIB Non-Small Cell Lung Cancer (IMpower030)

TARGETS
PD-L1

LOCATIONS: Colorado, Nebraska, Missouri, Minnesota, Arizona, Texas, Illinois

NCT03924869

PHASE 3

Efficacy and Safety Study of Stereotactic Body Radiotherapy (SBRT) With or Without Pembrolizumab (MK-3475) in Adults With Medically Inoperable Stage I or IIA Non-Small Cell Lung Cancer (NSCLC) (MK-3475-867/KEYNOTE-867)

TARGETS
PD-1

LOCATIONS: Colorado, South Dakota, North Dakota, Minnesota, Washington, California, Indiana, Tennessee

NCT04294810

PHASE 3

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT

LOCATIONS: Colorado, Minnesota, Texas, Illinois, Washington, Tennessee, Ohio, Florida, Virginia

NCT03822351

PHASE 2

Durvalumab Alone or in Combination With Novel Agents in Subjects With NSCLC

TARGETS
PD-L1, CD73, NKG2A

LOCATIONS: Colorado, Utah, Nebraska, Kansas, South Dakota, Texas, California

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NCT03446040

PHASE 1/2

An Investigational Immunotherapy Study of BMS-986258 Alone and in Combination With Nivolumab in Participants With Solid Cancers That Are Advanced or Have Spread

TARGETS
TIM-3, PD-1

LOCATIONS: Colorado, California, Tennessee, Edmonton (Canada), Michigan, Pennsylvania, Chuo-ku (Japan), Kobe-shi (Japan), Westmead (Australia)

NCT03459222

PHASE 1/2

An Investigational Study of Immunotherapy Combinations in Participants With Solid Cancers That Are Advanced or Have Spread

TARGETS
CTLA-4, PD-1, LAG-3

LOCATIONS: Colorado, Missouri, California, Tennessee, Maryland, Newcastle Upon Tyne (United Kingdom), Oxford (United Kingdom), Villejuif (France), Pamplona (Spain), Madrid (Spain)

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: Colorado, New Mexico, South Dakota, Oklahoma, Missouri, Arizona, Arkansas, Minnesota

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: Colorado, Texas, Washington, Oregon, Edmonton (Canada)

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: Colorado, Texas, Michigan, Ohio, Culiacan (Mexico), Florida, South Carolina, Maryland

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GENE
CCND1

ALTERATION
amplification - equivocal

RATIONALE
CCND1 amplification or overexpression may activate CDK4/6 and may predict sensitivity to CDK4/6 inhibitors.

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Colorado, Nebraska, Wyoming

NCT03237390

PHASE 1

Ribociclib and Gemcitabine Hydrochloride in Treating Patients With Advanced or Metastatic Solid Tumors

TARGETS
CDK6, CDK4

LOCATIONS: Arizona, Minnesota, Florida

NCT03099174

PHASE 1

This Study in Patients With Different Types of Cancer (Solid Tumours) Aims to Find a Safe Dose of Xentuzumab in Combination With Abemaciclib With or Without Hormonal Therapies. The Study Also Tests How Effective These Medicines Are in Patients With Lung and Breast Cancer.

TARGETS
CDK4, CDK6, IGF-1, IGF-2, Aromatase, ER

LOCATIONS: Nevada, Plerin Sur Mer (France), Tampere (Finland), Herlev (Denmark), København Ø (Denmark), Turku (Finland), Helsinki (Finland), Pozuelo de Alarcón (Spain), Madrid (Spain), Besançon (France)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03965845

PHASE 1/2

A Study of Telaglenastat (CB-839) in Combination With Palbociclib in Patients With Solid Tumors

TARGETS
CDK4, CDK6, GLS

LOCATIONS: Texas, Georgia

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NCT02791334

PHASE 1

A Study of Anti-PD-L1 Checkpoint Antibody (LY3300054) Alone and in Combination in Participants With Advanced Refractory Solid Tumors

TARGETS
CDK4, CDK6, PD-L1, MET, AXL, VEGFRs, TIM-3

LOCATIONS: Texas, Tennessee, Toronto (Canada), Edegem (Belgium), Brussels (Belgium), Villejuif Cedex (France), Bordeaux (France), Madrid (Spain), Seoul (Korea, Republic of)

NCT03310879

PHASE 2

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT02897375

PHASE 1

Palbociclib With Cisplatin or Carboplatin in Advanced Solid Tumors

TARGETS
CDK4, CDK6

LOCATIONS: Georgia

NCT03454035

PHASE 1

Ulixertinib/Palbociclib in Patients With Advanced Pancreatic and Other Solid Tumors

TARGETS
MAPK3, MAPK1, CDK4, CDK6

LOCATIONS: North Carolina

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GENE
KRAS

ALTERATION
G12F

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS alterations are not predictive biomarkers for MEK inhibitor monotherapy in NSCLC and combinatorial approaches may yield improved efficacy. Clinical evidence suggests that patients with KRAS-mutant NSCLC may be sensitive to the CDK4/6 inhibitor abemaciclib.

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Colorado, Oklahoma, Arizona, Texas, Wisconsin, California, Oregon

NCT03637491

PHASE 2

A Study of Avelumab, Binimetinib and Talazoparib in Patients With Locally Advanced or Metastatic RAS-mutant Solid Tumors

TARGETS
MEK, PARP, PD-L1

LOCATIONS: Colorado, Utah, Arkansas, California, Texas, Indiana, Pennsylvania, Gent (Belgium)

NCT03600701

PHASE 2

Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer

TARGETS
PD-L1, MEK

LOCATIONS: California, Ohio, Georgia, Virginia, Florida

NCT03225664

PHASE 1/2

BATTLE-2 Program - A Biomarker-Integrated Targeted Therapy in Non-Small Cell Lung Cancer (NSCLC)

TARGETS
PD-1, MEK

LOCATIONS: Texas

NCT03581487

PHASE 1/2

Durvalumab, Tremelimumab, and Selumetinib in Treating Participants With Recurrent or Stage IV Non-small Cell Lung Cancer

TARGETS
MEK, PD-L1, CTLA-4

LOCATIONS: Texas

NCT03099174

PHASE 1

This Study in Patients With Different Types of Cancer (Solid Tumours) Aims to Find a Safe Dose of Xentuzumab in Combination With Abemaciclib With or Without Hormonal Therapies. The Study Also Tests How Effective These Medicines Are in Patients With Lung and Breast Cancer.

TARGETS
CDK4, CDK6, IGF-1, IGF-2, Aromatase, ER

LOCATIONS: Nevada, Plerin Sur Mer (France), Tampere (Finland), Herlev (Denmark), København Ø (Denmark), Turku (Finland), Helsinki (Finland), Pozuelo de Alarcón (Spain), Madrid (Spain), Besançon (France)

Electronically signed by Julie Tse, M.D. | 13 July 2020
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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NCT02974725

PHASE 1

Study of LXH254 and LTT462 in NSCLC

TARGETS
CDK6, CDK4, ERK1, ERK2, ARAF, BRAF, MEK

LOCATIONS: California, Massachusetts, Stockholm (Sweden), Leuven (Belgium), Villejuif Cedex (France), Essen (Germany), Koeln (Germany), Pamplona (Spain), Madrid (Spain)

NCT03299088

PHASE 1

Pembrolizumab and Trametinib in Treating Patients With Stage IV Non-Small Cell Lung Cancer and KRAS Gene Mutations

TARGETS
MEK, PD-1

LOCATIONS: California

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

LOCATIONS: Texas

NCT03745989

PHASE 1

Study of MK-8353 + Selumetinib in Advanced/Metastatic Solid Tumors (MK-8353-014)

TARGETS
ERK1, ERK2, MEK

LOCATIONS: Texas, Vancouver (Canada), Toronto (Canada), Florida, Bellinzona (Switzerland)

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GENE
STK11

ALTERATION
I192fs*95

RATIONALE
Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations.

NCT01827384

PHASE 2

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

TARGETS
PARP, mTOR, MEK, WEE1

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

NCT02719691

PHASE 1

Phase I Study of MLN0128 and MLN8237 in Patients With Advanced Solid Tumors and Metastatic Triple-negative Breast Cancer

TARGETS
Aurora kinase A, mTORC1, mTORC2

LOCATIONS: Colorado

NCT03154294

PHASE 1

Evaluation of the Safety and Tolerability of TAK-228 With TAK-117 and Paclitaxel in Advanced Solid Tumors

TARGETS
PI3K-alpha, mTORC1, mTORC2

LOCATIONS: South Dakota

NCT03334617

PHASE 2

Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy.

TARGETS
PD-L1, PARP, mTORC1, mTORC2, ATR, CD73, STAT3

LOCATIONS: Missouri, California, Texas, Edmonton (Canada), Tennessee, Toronto (Canada), Maryland

NCT01737502

PHASE 1/2

Sirolimus and Auranofin in Treating Patients With Advanced or Recurrent Non-Small Cell Lung Cancer or Small Cell Lung Cancer

TARGETS
mTOR

LOCATIONS: Arizona

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

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NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
VEGFA, VEGFB, PIGF, mTORC1, mTORC2

LOCATIONS: Texas

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03430882

PHASE 1

Sapanisertib, Carboplatin, and Paclitaxel in Treating Patients With Recurrent or Refractory Malignant Solid Tumors

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

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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.

BCORL1
P531Q

ERBB2
L994F

GNAS
D172Y and T160fs*56

IGF1R
R437C

KEAP1
Y567D

KIT
E191K, E227K, M171I and splice site 338-1G>A

MPL
R102P

SMARCA4
E1483K

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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)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	Tabrecta™ (Capmatinib)
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)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre™ (Pemigatinib)
Prostate Cancer	Homologous Recombination Repair (*HRR*) gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*) alterations	Lynparza® (Olaparib)
Solid Tumors	*TMB* ≥ 10 mutations per megabase	Keytruda® (Pembrolizumab)

The median exon coverage for this sample is 725x

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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 2.14.0

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)

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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