FOUNDATIONONE®CDx

PATIENT

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

COUNTRY CODE
PE

REPORT DATE
14 Feb 2022

ORDERED TEST #
ORD-1288160-01

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

PATIENT
DISEASE Lung non-small cell lung carcinoma (NOS)
DATE OF BIRTH 12 June 1957
SEX Male
MEDICAL RECORD # Not given

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

SPECIMEN
SPECIMEN SITE Lung
SPECIMEN ID Q67617-1A
SPECIMEN TYPE Block
DATE OF COLLECTION 17 December 2021
SPECIMEN RECEIVED 19 January 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 9 Muts/Mb

Genomic Findings

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

CD274 (PD-L1) amplification
PDCD1LG2 (PD-L2) amplification
MET exon 14 splice site (2888-1G>C), amplification
ATM R337H
CDK4 amplification
CDK6 amplification
MDM2 amplification
CDKN2A/B p16INK4a loss and p14ARF loss exons 2-3
EPHB4 amplification
ERBB3 amplification
JAK2 amplification
SPEN A2804fs*5

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

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Atezolizumab** (p. 13), **Cemiplimab** (p. 14), **Durvalumab** (p. 16), **Nivolumab** (p. 17), **Nivolumab + Ipilimumab** (p. 17), **Pembrolizumab** (p. 18), **Capmatinib** (p. 14), **Crizotinib** (p. 15), **Tepotinib** (p. 19)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 23)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 9 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CD274 (PD-L1) - amplification	Atezolizumab 1	Avelumab
	Cemiplimab 1	
	Durvalumab 1	
	Nivolumab 1	
	Nivolumab + Ipilimumab 1	
	Pembrolizumab 1	
10 Trials see p. 25	Dostarlimab	
PDCD1LG2 (PD-L2) - amplification	Atezolizumab 1	Avelumab
	Cemiplimab 1	
	Durvalumab 1	
	Nivolumab 1	
	Pembrolizumab 1	
10 Trials see p. 34	Dostarlimab	
MET - exon 14 splice site (2888-1G>C), amplification	Capmatinib 2A	Cabozantinib
	Crizotinib 2A	
10 Trials see p. 32	Tepotinib 2A	
ATM - R337H	none	Niraparib
		Olaparib
		Rucaparib
10 Trials see p. 23		Talazoparib
CDK4 - amplification	none	none
10 Trials see p. 27		
CDK6 - amplification	none	none
10 Trials see p. 29		
MDM2 - amplification	none	none
4 Trials see p. 31		

1 NCCN category

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

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 approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

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

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. 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[6]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2021).

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[16]. 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[16-18]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER

Tumor Mutational Burden

RESULT
9 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 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 (based on this assay or others); 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 (based on this assay or others);[22-23,26-28,32-39]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[40], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[41], 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[42]. 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[43]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[44-45], several other large studies did find a strong association with increased TMB[46-49]. 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[50]. 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)[44]. 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[51]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[51-52].

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[53-54] and cigarette smoke in lung cancer[32,55], treatment with temozolomide-based chemotherapy in glioma[56-57], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[58-62], and microsatellite instability (MSI)[58,61-62]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[22-23,26-28,32-39,63].

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

GENE
CD274 (PD-L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of strong clinical evidence, CD274 amplification and PD-L1 overexpression may predict sensitivity to antibodies targeting PD-L1 or PD-1. Patients with high tumor PD-L1 expression across multiple solid tumor types have exhibited improved OS with the PD-L1 antibody atezolizumab[64-65]. Compared with PD-L1-negative patients, clinical studies with the PD-L1 antibody durvalumab have suggested higher response rates for patients with PD-L1-positive tumor or immune cells and urothelial carcinoma[66], non-small cell lung cancer (NSCLC)[67-68] , or head and neck squamous cell carcinoma[69-70] . The PD-1 antibodies pembrolizumab and nivolumab (alone or in combination with ipilimumab) have elicited significant clinical responses in solid tumors[71-73], and for patients with Hodgkin lymphoma, a tumor type that harbors frequent PD-L1 copy number gains[74]. Clinical studies have reported that PD-L1 amplification[71] or expression[75] in solid tumors is associated with response to anti-PD-1 antibodies. However, a study evaluating nivolumab in patients with urothelial carcinoma observed no correlation between OS benefit and PD-L1 expression levels[76]. A Phase 1 trial evaluating bintrafusp alfa, a fusion protein targeting TGF-beta and PD-L1, in the second line setting for patients with NSCLC reported ORRs of 36% (10/27) and 86% (6/7) for patients with PD-L1-positive and PD-L1-high expression, respectively[77]. JAK2 has been reported as important for PD-L1 expression in Hodgkin lymphoma and primary mediastinal B-cell lymphoma cell lines, and JAK2 inhibition has been reported to decrease PD-L1 transcript accumulation[78-79]. Therefore, JAK2 inhibitors such as ruxolitinib may also be relevant for a patient with PD-L1 amplification.

FREQUENCY & PROGNOSIS

CD274 amplification has been reported in 1-2% of cases in the Lung Adenocarcinoma and Lung Squamous Cell Carcinoma TCGA datasets[80-81]. Higher PD-L1 expression in non-small cell lung cancer (NSCLC) has been correlated with poor patient prognosis in multiple studies[82-84].

FINDING SUMMARY

CD274 encodes the programmed cell death ligand 1 (PD-L1), also known as B7-H1, which is a cell surface molecule important for regulating the activity of T-cells through binding to various T-cell receptors. Although PD-L1 is a costimulatory molecule for naive T-cells, it can provide inhibitory signals to activated T-cells through interactions with the receptors PD-1 or CD80[85-86]. These signals can help PD-L1-expressing tumor cells evade immune detection by natural killer cells or T-cells[87-89]. CD274 amplification is associated with positive PD-L1 protein expression in solid tumors[90-92] and lymphomas[74,78].

GENE
MET

ALTERATION
exon 14 splice site (2888-1G>C), amplification

TRANSCRIPT ID
NM_000245

CODING SEQUENCE EFFECT
2888-1G>C

VARIANT ALLELE FREQUENCY (% VAF)
85.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[93-96], gastroesophageal cancer[97], glioblastoma[98], and carcinoma of unknown primary[99]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified NSCLC both as a monotherapy[100-101] and in combination with an EGFR-TKI for patients with concurrent activating EGFR mutations[102-104]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[105] and NSCLC[106] as a monotherapy, as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[107-109] . Savolitinib elicited responses in patients with MET-amplified papillary renal cell carcinoma[110] and gastric cancer either alone or in combination with docetaxel[111-112]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[113]. Patients with MET-amplified NSCLC[114] or MET-amplified gastric cancer[115] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapies such as the monoclonal HGF-targeting antibody rilotumumab, as well as the combination of ramucirumab and the monoclonal MET-targeting antibody emibetuzumab[116]. A first-in-human Phase 1 trial of telisotuzumab vedotin (teliso-V), a MET antibody-drug conjugate, reported activity in a subset of patients with MET-positive NSCLC, with an ORR of 19% (3/16) and a DCR of 56% (9/16); no responses were observed in any other patients[117]. A subsequent Phase 2 trial of teliso-V in patients with MET-positive NSCLC reported a 35% (13/37) ORR in patients with non-squamous, EGFR-wildtype tumors, which met the prespecified criteria for transition to the next stage; lower ORRs were observed in patients with squamous (14%; 3/21) or non-squamous EGFR-mutated (13%; 4/30) tumors[118]. MET inhibitors crizotinib, capmatinib, PF-04217903, tepotinib, glesatinib, savolitinib, and foretinib have provided benefit for patients with MET-mutated papillary renal cell carcinoma (RCC)[119-122], histiocytic sarcoma[123], and non-small cell lung cancer (NSCLC) of varied histologies[124-128]. Patients with MET exon 14 mutated NSCLC who were treated with 1 of several MET inhibitors exhibited superior outcomes (median OS 24.6 vs. 8.1 months; HR=0.11, p=0.04) compared with patients who were not treated with a MET inhibitor[129]. Tepotinib showed durable clinical activity in patients with NSCLC with MET exon 14 skipping mutations[130], and yielded a PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC[131]. In another study, 11 patients with hereditary papillary RCC and germline MET mutations (4 of which were H1094R) experienced 5 PRs and 5 SDs after treatment with foretinib[119]. Savolitinib yielded ORRs of 49% (30/61) in patients with MET exon 14 mutated NSCLC[132] and numerically higher ORR for patients with MET-driven papillary RCC compared to sunitinib (27% [9/33] vs. 7.4% [2/27])[122]. A Phase 1 study for patients with MET-altered NSCLC treated with MET inhibitor bozitinib monotherapy reported an overall ORR of 30.6% (11/36) and DCR of 97.2% (35/36) with MET overexpression, amplification, and exon 14 skipping demonstrating ORRs of 35.7% (5/14), 41.2% (7/17), and 66.7% (10/15), respectively; increased ORRs were observed in patients with both exon 14 skipping and amplification (100%, 4/4) and with both amplification and overexpression (50%, 3/6)[133]. A Phase 2 study evaluating the MET inhibitor savolitinib for patients with MET exon 14 splice site mutation-positive pulmonary sarcomatoid carcinoma and other types of non-small cell lung cancer (NSCLC) reported that 52% (16/31) of patients achieved a PR[134]. In the Phase 1 CHRYSALIS study, patients with NSCLC harboring MET exon 14 skipping mutations treated with amivantamab achieved a 64% (9/14; 5 PRs confirmed, 4 PRs pending) unconfirmed ORR; 4 out of 7 patients previously treated with MET TKIs responded (Spira et al., 2021 WCLC Abstract OA15.03).

FREQUENCY & PROGNOSIS

In the Phase 2 VISION study of patients with non-small cell lung cancer, MET exon 14 skipping alterations were reported in 3.6% of patients[135]. In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in 3% of samples[123]. In TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[80-81]. MET amplification has been reported at incidences of 14-48% in non-small cell lung cancer (NSCLC), is correlated with increased MET protein expression, and occurs more frequently following treatment with EGFR inhibitors[114,136-143]. In the Phase 2 VISION study of patients with NSCLC, MET amplification was reported in 4.9% of samples[135]. Studies on the effect of MET amplification on prognosis in NSCLC have yielded conflicting results[136,140-141,144-148], although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[149]. MET exon 14 splice alteration, which has predominantly been observed in lung cancer, was found to be an independent poor prognostic factor in a study of 687 patients with NSCLC[150]. However, other studies did not find MET exon 14 splice alteration as a major risk factor for overall survival for NSCLC patients, although recurrence rate was significantly higher in patients with exon 14 splice alteration compared to those with ALK fusion[151-152]. Among NSCLC patients with exon 14 alterations that had not been previously treated with a MET inhibitor, a non-significant trend for reduced survival was noted in the context of concurrent MET amplification (5.2 vs 10.5 months, p = 0.06)[129].

FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[153-154]. MET has been reported to be amplified in cancer[155], with amplification positively correlating with protein expression in some cancer types[136,156-159] and associating with therapeutic response to MET inhibitors in a variety of cancer types[93-95,97-99,160-161]. Certain MET alterations have been associated with the removal of exon

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

14[125,162-166] and/or loss of a binding site for the ubiquitin ligase CBL, an enzyme that targets MET for degradation[162,167-169]. Loss of either MET exon 14 or a CBL binding site increases MET stability, leading to prolonged signaling upon HGF stimulation and increased oncogenic potential[162,166,168-172]; these mutations are expected to be activating. Responses to various MET inhibitors have been reported for multiple patients with alterations in their tumors predicted to lack MET exon 14[123,125,173-177].

GENE

PDCD1LG2 (PD-L2)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PDCD1LG2 amplification, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-1, PD-L1, or PD-L2 antibodies. The PD-1 antibodies pembrolizumab and nivolumab have elicited significant clinical responses in several cancer types, including melanoma, NSCLC, renal cell carcinoma[178-186], and Hodgkin lymphoma, which harbors frequent PD-L2 copy number gains[74,187]. The PD-L1 antibody atezolizumab does not block interaction between PD-1 and PD-L2; however, multiple clinical studies with atezolizumab have reported an association between increased PD-L2 expression and response or improved overall survival in multiple solid tumor types, thereby suggesting that PD-L2 overexpression may serve as a biomarker of response[64-65,188]. Additionally, JAK2 has been reported as important for PD-L2 expression in Hodgkin lymphoma and PMBCL cell lines, and JAK2 inhibition has been reported to decrease PD-L2 transcript accumulation in preclinical studies[78-79]. Therefore, JAK2 inhibitors may also be relevant for a patient with PD-L2 amplification. Ruxolitinib is a kinase inhibitor that targets JAK1 and JAK2 and is approved to treat intermediate or high-risk myelofibrosis[189].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PDCD1LG2 amplification was observed in 3% of lung squamous cell carcinoma (SCC) cases[81] and <1% of cases in the Lung Adenocarcinoma TCGA dataset[80]. PD-L2 was found to be expressed in approximately 50% of lung adenocarcinoma tumors and to predict poor overall survival, independently of PD-L1 expression[190]. PD-L2 protein expression was observed in 24% of pulmonary SCC samples and expression was more frequent (93.5%) in metastatic lymph node tumors; PD-L2 expression was not significantly associated with prognosis in this study[191].

FINDING SUMMARY

PDCD1LG2 encodes the programmed cell death 1 ligand 2 (PD-L2), also known as CD273, PD-L2, and B7-DC, which is essential for T-cell proliferation and interferon production. PD-1 signaling, which can be stimulated by PD-L2, results in 'T-cell exhaustion', a temporary inhibition of activation and proliferation that can be reversed on removal of the PD-1 signal[85-86]. Amplification of PDCD1LG2 and the adjacent locus CD274, encoding PD-L1, has been reported in 29% of primary mediastinal B-cell lymphoma (PMBCL) cases, and PDCD1LG2 copy number gain has been reported to correlate with increased PD-L2 protein expression as determined by immunohistochemistry[192-193].

GENE
ATM

ALTERATION
R337H

TRANSCRIPT ID
NM_000051

CODING SEQUENCE EFFECT
1010G>A

VARIANT ALLELE FREQUENCY (% VAF)
31.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[194]. Clinical data in prostate cancer[195-197], gastric cancer[198], colorectal cancer[199], breast cancer[199], papillary renal cell carcinoma[200], and cholangiocarcinoma[201] indicate that loss or inactivation of ATM may confer sensitivity to PARP inhibitors[202-209]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[210] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[211] harbored ATM inactivation or protein loss; studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[212-214] and hematologic malignancies[212,215] also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity[216]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

ATM mutations have been reported in 8-11% of lung adenocarcinomas[47-48,80] and 5% of lung squamous cell carcinomas (SCCs)[81]. In one study, higher ATM protein levels in lung SCC, but not in lung adenocarcinoma, significantly correlated with shorter disease-free and overall survival of patients treated with cisplatin[217].

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response[218]. Loss of functional ATM promotes tumorigenesis[219]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

ATM mutation carriers have increased cancer risk, with female carriers displaying a 38% lifetime risk of breast cancer[220]. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome[221]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[218,221]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[221]. In the appropriate clinical context, germline testing of ATM is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[222-227]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[226,228-229]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
CDK4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib[230-233]. Clinical benefit has been reported for limited tumor types including patients with CDK4-amplified liposarcoma and sarcoma in response to treatment with abemaciclib[234], palbociclib[230,235], and ribociclib[236].

FREQUENCY & PROGNOSIS

In the TCGA datasets, CDK4 amplification or mutation occurs in 7% and 1% of lung adenocarcinoma cases, respectively[237]; however, neither were detected in any of the lung squamous cell carcinoma cases[81]. CDK4 amplification correlated with high CDK4 gene and protein expression in lung tumors[238]. High CDK4 protein expression has been detected in 23-47% of non-small cell lung cancers, specifically in 38% (18/47) of lung adenocarcinomas, 44% (4/9) of lung squamous cell carcinomas, and 83% (10/12) of large cell lung cancers[238-240]. A preclinical study suggests targeting of CDK4 as a potential strategy against KRAS-driven lung adenocarcinomas[241]. High CDK4 protein expression predicted poor overall survival in patients with lung cancer in one study[240].

FINDING SUMMARY

CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[242]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[243-244]. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein[230,238,245-250].

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

GENE
CDK6

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Tumors with CDK6 activation may be sensitive to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[231-232,251-252]. Clinical benefit has been reported for patients with CDK6-amplified or mutated solid tumors in response to treatment with ribociclib[236,253] .

FREQUENCY & PROGNOSIS

CDK6 alterations, including amplification or mutation, occur in 3% of lung adenocarcinoma cases and 4% of lung squamous cell carcinoma cases[80-81]. Amplification of chromosome 7q21, where CDK6 is located, was also reported in 8% of non-small cell lung carcinomas (NSCLC)[254]. Increased CDK6 protein has been detected in NSCLC samples and did not associate with tumor metastasis or overall patient survival in one study[255-256].

FINDING SUMMARY

CDK6 encodes cyclin-dependent kinase 6, which regulates the cell cycle, differentiation, senescence, and apoptosis[242,257-258]. CDK6 and its functional homolog CDK4 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[243-244]. Amplification of the chromosomal region that includes CDK6 has been reported in multiple cancer types, and has been associated with overexpression of CDK6 protein[259-260].

GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[261]. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[262-263]. Preliminary Phase 1 studies of the MDM2-p53 antagonist alrizomadlin (APG-115) reported a PR in a patient with liposarcoma harboring an MDM2 amplification and wildtype for TP53 and SD in 21%–38% (6/28 and 5/13, respectively) of patients in genomically unselected solid tumors[264-265] . A Phase 2 trial of alrizomadlin in combination with pembrolizumab reported a PR in 1 of 3 patients with malignant peripheral nerve sheath tumor that had failed standard therapy, as well as PRs in patients with multiple types of solid tumors that had failed immunotherapy, including 1 out of 14 patients with non-small cell lung cancer; 1 out of 5 patients with urothelial carcinoma; and 2 out of5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively[266]. Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively[267-268] ; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[269]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wildtype peripheral T-cell lymphoma in a Phase 2 study[270]; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[271-272] .

FREQUENCY & PROGNOSIS

In the TCGA datasets, amplification of MDM2 has been reported in 8% of lung adenocarcinoma cases[80] and 2% of lung squamous cell carcinoma cases[81]. Separate studies have reported MDM2 amplification at similar incidences of 6-7% in non-small cell lung cancer (NSCLC), mainly in patients with adenocarcinoma, but a higher incidence of 21% (24/116) has also been observed, with amplification found in various NSCLC subtypes[273-275]. The role of MDM2 expression/amplification as a prognostic marker is complex, with some studies showing a negative and others a positive effect on survival in patients with NSCLC[273,275-277].

FINDING SUMMARY

MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[278-280]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[281-282]. Overexpression or amplification of MDM2 is frequent in cancer[283]. Although two retrospective clinical studies suggest that MDM2 amplification may predict a short time-to-treatment failure on anti-PD-1/PD-L1 immune checkpoint inhibitors, with 4/5 patients with MDM2 amplification[284] and 2/3 patients with MDM2 or MDM4 amplification[285] experiencing tumor hyperprogression, amplification of MDM2 or MDM4 was not associated with shorter progression-free survival (PFS) in a retrospective analysis of non-small cell lung cancer (NSCLC) outcomes with immune checkpoint inhibitors (hazard ratio of 1.4, p=0.44)[36]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[36].

GENE
CDKN2A/B

ALTERATION
p16INK4a loss and p14ARF loss exons 2-3

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[286-289]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[290-291], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[233,236,251,253,292-294]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[263,295], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[80]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[81]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples[81,296-301]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[298,302-304].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[305-306]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[297,307]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[308-309]. One or more alterations observed here are predicted to result in p16INK4a loss of function[310-331]. One or more alterations seen here are predicted to result in p14ARF loss of function[314,331-334].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[335]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[336-337]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[338-340]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[341-343]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
EPHB4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies available to target EPHB4 alterations in cancer. sEPHB4 is a soluble monomeric extracellular domain of EPHB4 that functions as an antagonist of EphrinB2-EPHB4 interaction[344], and fusion of sEPHB4 with human serum albumin (HSA) increases its stability[345]. Recombinant sEPHB4-HSA is under investigation in clinical trials. Preclinical studies have demonstrated that sEPHB4-HSA inhibits cell proliferation and xenograft tumor growth, including for cells expressing cancer-associated EPHB4 mutants or overexpressing wild-type EPHB4[344,346-350]. In addition, small-molecule inhibitors targeting multiple tyrosine kinases including EPHB4, such as JI-101 and XL647, have been under preclinical and clinical investigation[351-353].

FREQUENCY & PROGNOSIS

Increased EPHB4 mRNA and/or protein expression has been reported in a variety of cancer types, including head and neck squamous cell carcinoma (HNSCC)[354-357], gastric and esophageal[358-362], colorectal carcinoma (CRC)[363-369], breast[370-374], ovarian[374-376], endometrial[377-379], thyroid[380-382], lung[383-384], glioma[385-386], and other solid tumors[346,387-394]. In several of these studies, increased EPHB4 expression has been associated with clinicopathologic features, including disease stage[346,354,370,375-376,384,387,389], histological grade[360,370,377,386], and hormone receptor status[373,378]. High EPHB4 expression has been associated with inferior survival in multivariate analyses for patients with CRC treated with bevacizumab [hazard ratio (HR) = 5.95][368], HNSCC (HR = 2.95)[357], epithelial ovarian cancer (HR = 4.53)[374], or glioma (HR = 3.21)[386].

FINDING SUMMARY

EPHB4 encodes a member of the EPH family of receptor tyrosine kinases[395]. Ephrin signaling has been implicated in multiple processes, including cell adhesion, cytoskeletal organization, and cell migration[396], and signaling between EPHB4 and its ligand EphrinB2 is particularly important for angiogenesis[397-398]. EPHB receptors, including EPHB4, have been shown to undergo dysregulation (amplification, mutation, under- or overexpression) in a number of different cancer types[399]. EPHB4 amplification has been reported in several solid tumor types[354-355,360,400-401] and was associated with advanced disease stage in head and neck squamous cell carcinoma (HNSCC)[354]. Activating missense mutations in or near the tyrosine kinase domain, including G723S, A742V, and P881S, have also been identified in lung cancer[350].

GENE
ERBB3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

ERBB3 cooperates with other ERBB family members, in particular ERBB2, for efficient signaling[402-405]. Therefore, ERBB3 amplification or activating mutation may predict sensitivity to therapies targeting ERBB2, including antibodies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), and dual EGFR/HER2 TKIs such as lapatinib and afatinib. Clinical and preclinical data support sensitivity of ERBB3 activating mutations to various anti-ERBB2 agents[404,406-410], but data are generally limited for ERBB3 amplification. Biomarker analyses of several Phase 3 trials have not identified an association of ERBB3 expression levels with benefit from trastuzumab-, pertuzumab-, or T-DM1-containing regimens in HER2-positive breast cancer[411-414], T-DM1 in HER2-positive gastric and gastroesophageal junction (GEJ) cancer[415], pertuzumab combined with chemotherapy in ovarian cancer[416], or afatinib in HNSCC[417]. Similarly, ERBB3 expression levels were not associated with PFS or OS from lapatinib plus capecitabine in a Phase 2 study of gastric/GEJ cancer[418] or in retrospective studies of HER2-positive breast cancer[419-421].

FREQUENCY & PROGNOSIS

ERBB3 has been reported to be amplified in 0-3% of non-small cell lung carcinomas (NSCLCs)[80-81,422]. However, ERBB3 mRNA has been detected in over 75% of NSCLC tumors[423] and ERBB3 protein expression has been reported in 51% (32/63) of lung squamous cell carcinomas, compared to 18% (9/51) of lung adenocarcinomas and 9% (1/11) of large cell carcinomas[424], whereas a conflicting study reported higher ERBB3 mRNA expression in lung adenocarcinoma compared to squamous cell carcinoma[425]. High-level expression of ERBB3 mRNA has been associated with distant site metastases and poor overall survival in NSCLC[423].

FINDING SUMMARY

ERBB3 (also known as HER3) encodes a member of the epidermal growth factor receptor (EGFR) family[426]. One study has demonstrated a weak but significant association between ERBB3 gene amplification and ERBB3 protein expression in breast cancer tissue[427].

GENE
JAK2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

While JAK2 inhibitors have shown clinical benefit in hematological malignancies, clinical utility in solid tumors has not been demonstrated.

FREQUENCY & PROGNOSIS

Amplification of JAK2 has rarely been reported in lung cancer, detected in 2% and 1% in the lung adenocarcinoma and lung squamous cell carcinoma TCGA datasets, respectively[80-81]. Increased expression and activity of JAK2 has been reported in non-small cell lung cancer (NSCLC), cited in 57-79% of cases, and has been correlated with activation of the STAT3 pathway[428-429]. High expression of the JAK2-STAT3 pathway has been associated with decreased survival in patients with NSCLC[429].

FINDING SUMMARY

JAK2 encodes Janus kinase 2, a tyrosine kinase that regulates signals triggered by cytokines and growth factors[430]. JAK2 is often mutated in hematopoietic and lymphoid cancers. Cell lines and primary lymphoid cancer cells from a small number of patients with JAK2 amplification exhibit overabundance of JAK2 mRNA, protein, and phosphorylated JAK2 targets and respond to JAK2 inhibitors such as ruxolitinib similarly to JAK2-rearranged (activated) cell lines and primary blood cells from patients[78,431].

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

GENE
SPEN

ALTERATION
A2804fs*5

TRANSCRIPT ID
NM_015001

CODING SEQUENCE EFFECT
8406delA

VARIANT ALLELE FREQUENCY (% VAF)
12.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address SPEN inactivating mutations. Although gamma-secretase inhibitors are in clinical development to target NOTCH activation, it is not known if these therapies would be beneficial in the context of SPEN mutation.

FREQUENCY & PROGNOSIS

SPEN truncating mutations have been reported in adenoid cystic carcinoma (ACC) (21%)[432] and splenic marginal zone lymphoma (SMZL) (5%)[433]; NOTCH pathway gene mutations were frequent in both ACC and SMZL and observed in approximately 30% of cases[432-433].

FINDING SUMMARY

SPEN (also known as MINT or SHARP) encodes a transcriptional regulator that interacts with HDAC1 and the SMRT/NcoR corepressors[434-435]. SPEN represses the transcriptional activity of the NOTCH signaling pathway[436-437]. Activation of NOTCH signaling results in binding of the transcription factor RBPJ to the NOTCH intracellular domain and consequent activation of the NOTCH transcriptional program[438]. SPEN binding to RBPJ has been shown to repress NOTCH-mediated transcription[436-437]. SPEN alterations that result in loss of the RBPJ-interaction domain (aa 2804-2816)[436-437] or the SPOC domain (aa 3498-3664)[435] are predicted to disrupt binding of SPEN to RBPJ or corepressors and are likely to be inactivating.

Atezolizumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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, hepatocellular carcinoma, and BRAF V600-positive melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangements, that lead to overexpression of PD-L1 may predict sensitivity to atezolizumab based on clinical evidence in multiple solid tumor types[64,188,439] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to anti-PD-L1 inhibitors such as atezolizumab. Although atezolizumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to atezolizumab[64,188,439] .

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[440]. 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[441-443] . 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[442]. 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[441]. 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[443]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic non-small cell lung cancer (NSCLC) reported improved median OS (mOS; 20.2 vs. 13.1 months, HR=0.59), median PFS (8.1 vs. 5.0 months), and ORR (38% vs. 29%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[444]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in mOS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[445], confirming previous Phase 2 trial data[64,446] . In the OAK trial, improved OS was observed for patients, regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was reported for patients with high PD-L1 tumor cell (>50%) or tumor-infiltrating immune cell (>10%) expression (HR=0.41) compared with those possessing <1% expression on either cell type (HR=0.75)[445]. Retrospective analyses of the OAK trial also identified clinical benefit for patients receiving atezolizumab and metformin compared with atezolizumab alone (ORR of 25% vs. 13%)[447], and for patients with 2 or more mutations in DNA damage response and repair pathway genes compared with those without (durable clinical benefit rate of 57% vs. 31%, p=0.003)[448]. The Phase 3 IMpower010 study of adjuvant atezolizumab treatment following adjuvant chemotherapy for patients with resected Stage II-IIIA NSCLC reported improved median disease-free survival compared with best supportive care (42.3 vs. 35.3 months, HR=0.79), with the greatest benefit observed for patients with PD-L1 tumor cell expression of ≥1% (not reached vs. 35.3 months, HR=0.66)[449]. In the randomized Phase 2 CITYSCAPE study of treatment-naive advanced NSCLC, the addition of tiragolumab to atezolizumab showed clinically meaningful improvement in ORR (37% [25/67] vs. 21% [14/68]) and PFS (5.6 vs. 3.9 months, HR=0.58), with greater ORR (66% [19/29] vs. 24% [7/29]) and PFS (not reached vs. 4.1 months, HR=0.30) observed for patients with PD-L1 tumor proportion scores (TPS) ≥50%[450].

Capmatinib

Assay findings association

MET
exon 14 splice site (2888-1G>C), amplification

AREAS OF THERAPEUTIC USE

Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[100,130,132,451-453] , MET mutations associated with exon 14 skipping may predict sensitivity to selective MET inhibitors. On the basis of clinical data in non-small cell lung cancer[100,106-109,454] , hepatocellular carcinoma[105], renal cell carcinoma[110], and gastric cancer[111], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Capmatinib monotherapy has demonstrated clinical activity for patients with advanced NSCLC harboring MET exon 14 skipping alterations and lacking EGFR mutations or ALK rearrangements[455-456] . The Phase 2 GEOMETRY mono-1 study reported a higher ORR (67.9% vs. 40.6%) and DCR (96.4% vs. 78.3%), and longer PFS (12.4 vs. 5.4 months) and median duration of response (12.6 vs. 9.7 months) for treatment-naive patients with exon 14 mutations when compared with those who were previously treated; no correlation was observed between patient responses and the presence of co-occurring MET amplification[451]. Additionally, this study recorded a 53.8% (7/13) intracranial response rate and 92.3% (12/13) intracranial DCR[455]. A retrospective analysis of the GEOMETRY mono-1 study compared with a cohort of real-world (RW) patients with NSCLC harboring MET exon 14 skipping alterations who received first-line chemotherapy and/or immunotherapy reported a longer PFS (mPFS 12.0 vs mrwPFS 6.2 months) for patients that received capmatinib compared to chemotherapy and/or immunotherapy used in the real-world[457]. In the Phase 2 GEOMETRY mono-1 study for patients with advanced NSCLC and MET gene copy number (GCN) ≥10, capmatinib elicited ORRs of 29–40%, median PFS of 4.1–4.2 months, and median OS of 9.6–10.6 months across treatment-naive and previously treated cohorts[458]. A Phase 1 study of capmatinib monotherapy for advanced EGFR- and ALK-wild-type NSCLC reported ORRs of 46.7% (7/15) for patients with MET GCN ≥6, 25% (3/12) for patients with MET GCN 4–6, and 5.9% (1/17) for patients with MET GCN <4; median PFS was 3.7 months overall, and 7.9 months for patients with MET GCN ≥6[456]. Multiple Phase 1 and 2 clinical studies have reported limited efficacy for capmatinib monotherapy in non-NSCLC indications, with no responses observed for patients with glioblastoma (n=10)[459], gastric cancer (n=9), or other advanced solid tumors (n=24)[460-461] .

Cemiplimab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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 NSCLC with high PD-L1 expression (TPS ≥ 50%), cutaneous squamous cell carcinoma (CSCC), or basal cell carcinoma (BCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s). In multiple cancer types, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as improved clinical benefit in response to anti-PD-1 immunotherapies[74-75,187,462-466] and may predict sensitivity to cemiplimab.

SUPPORTING DATA

The Phase 3 EMPOWER-Lung 1 trial for treatment-naive advanced non-small cell lung cancer (NSCLC) reported that cemiplimab improved median PFS (mPFS, 8.2 vs. 5.7 months, hazard ratio [HR]=0.54), median OS (mOS, not reached vs. 14.2 months, HR=0.57), and ORR (39% vs. 20%) compared with chemotherapy in patients with high PD-L1 expression (TPS ≥ 50%); improved mPFS (6.2 vs. 5.6 months, HR=0.59), mOS (22.1 vs. 14.3 months, HR=0.68), and ORR (37% vs. 21%) were also reported for cemiplimab over chemotherapy in the intention-to-treat population[467]. In a Phase 2 trial of cemiplimab-containing regimens as second-line therapy for NSCLC, cemiplimab combined with ipilimumab elicited a numerically higher ORR (46% [5/11]) compared with high-dose (11% [1/9]) and standard-dose cemiplimab monotherapy (0% [0/8])[468].

Crizotinib

Assay findings association

MET
exon 14 splice site (2888-1G>C), amplification

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), and to treat pediatric and young adult patients with ALK rearrangement-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[93-95,469-470] , gastric cancer[160], gastroesophageal cancer[97], glioblastoma[98], and carcinoma of unknown primary[99], as well as in patients with MET-mutated cancers, including NSCLC[123,125-128,471] , renal cell carcinoma (RCC)[121], and histiocytic sarcoma[123]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[123,125-129] .

SUPPORTING DATA

The expansion cohort of the PROFILE 1001 study reported a 32.3% (21/65, 3 CRs) ORR, 7.3 month median PFS, and 20.5 month median OS for patients with advanced MET exon 14-altered NSCLC[472]. Other Phase 2 studies have reported ORRs of 20.0% to 35.7%, median PFS of 2.4 to 2.6 months, and median OS of 3.8 to 8.1 months for patients with MET-mutated NSCLC[473-474] . A retrospective study reported median PFS of 7.4 months in patients with MET exon 14-altered NSCLC treated with crizotinib[475]. In a small study for patients with NSCLC and MET overexpression with or without gene amplification, crizotinib elicited 11 PRs and 3 SDs in 19 evaluable patients[470]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[476-480] , ROS1 rearrangements[474,481-484] , an NTRK1 fusion[485], or MET activation[93-95,125-128,165,469-471,486-491] . The Phase 2 METROS and AcSe trials have reported ORRs of 31.3% to 32.0%, median PFS of 3.2 to 5.0 months, and median OS of 5.4 to 7.7 months for patients with MET amplified advanced non-small cell lung cancer (NSCLC); a higher level of amplification was predictive of better response in the AcSe trial (P=0.04)[473-474] . Additional patients with MET amplified NSCLC have been reported to experience clinical benefit from crizotinib in several case studies[93-95,489,491-492] . A patient with lung adenocarcinoma harboring K860I and L858R EGFR mutations, who acquired both EGFR T790M and MET amplification upon various treatments, experienced clinical benefit from subsequent combination treatment of osimertinib and crizotinib[493]. Two patients with ALK-positive NSCLC and acquired MET amplification experienced benefit from crizotinib monotherapy and crizotinib in combination with lorlatinib[494].

Dostarlimab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

Dostarlimab 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 response. It is FDA approved to treat patients with mismatch repair deficient recurrent or advanced endometrial cancer or solid tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation of PDCD1LG2 may lead to overexpression of PD-L2 and may confer sensitivity to PD-1 inhibitors such as dostarlimab. CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as dostarlimab based on clinical evidence in multiple solid tumor types[495-498] .

SUPPORTING DATA

In the Phase 1 GARNET trial of dostarlimab, patients with non-small cell lung cancer (NSCLC) experienced an immune-related ORR (irORR) of 27% with 2 CRs[496]. Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[495,497,499] . In the Phase 1 GARNET trial, single-agent dostarlimab elicited an ORR of 39% (41/106) and an immune-related ORR of 46% (50/110) for patients with non-endometrial dMMR solid tumors[497,500] .

Durvalumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as durvalumab based on clinical evidence in multiple solid tumor types[64,66-70,188,439,501-505] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as durvalumab. Although durvalumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to the similar PD-L1-blocking antibody atezolizumab[64,188,439] .

SUPPORTING DATA

In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable non-small cell lung cancer (NSCLC) who did not have progression on chemoradiotherapy, durvalumab monotherapy improved PFS versus placebo across PD-L1 expression subgroups; median PFS (mPFS) was 23.9 versus 5.6 months (HR=0.49) for patients with PD-L1 expression ≥1% and 10.7 versus 5.6 months (HR=0.79) for patients with PD-L1 expression <1%. Median OS (mOS) benefit was observed for patients with PD-L1 expression ≥1% (57.4 vs. 29.6 months, HR=0.60), but not for those with PD-L1 expression <1% (33.9 vs. 43.0 months, HR=1.05)[506-507] . 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 the investigator's choice of standard of care (SOC) for patients in cohort A (PD-L1 ≥25%)[508]. 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%)[508]. 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 vs. HR=0.85); however, patients with blood tumor mutational burden (bTMB) ≥20 Muts/Mb showed improved OS for durvalumab plus tremelimumab versus chemotherapy (21.9 vs. 10.0 months, HR=0.49)[509]. In the Phase 3 POSEIDON trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC, the addition of durvalumab and tremelimumab to chemotherapy improved mOS (14.0 vs. 11.7 months, HR=0.77) and mPFS (6.2 vs 4.8 months, HR=0.72) versus chemotherapy[510]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[511-512] and OS[511] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90%) had an ORR of 31% (21/68) compared with ORRs of 16% (24/146) for patients with ≥25% and 7.5% (7/93) for patients with <25% PD-L1 positivity[512]. Re-treatment with durvalumab for patients with PD-L1-positive (≥25%) EGFR-negative or ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or SD for 25% (10/40) of patients[513].

Nivolumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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 as monotherapy 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, classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma or squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). It is also approved in combination with cabozantinib to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to nivolumab. In various advanced solid tumors, including melanoma, lung, kidney, prostate, and colorectal cancer, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as with objective response to nivolumab[75,466] .

SUPPORTING DATA

For patients with platinum-refractory non-squamous non-small cell lung cancer (NSCLC), nivolumab improved median OS (mOS; 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)[184]. In advanced squamous NSCLC, second-line nivolumab resulted in longer mOS (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[183,185] . 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% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[514]. In the CheckMate 227 study, the combination of nivolumab and platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[515], despite Phase 1 results in the same setting suggesting improved ORR and OS[516]. In the Phase 3 CheckMate 816 study, the combination of nivolumab and platinum-based doublet chemotherapy did show benefit as a neoadjuvant treatment for patients with resectable NSCLC, reporting a pathological CR (pCR) rate of 24% versus 2.2% for chemotherapy alone, and the benefit was consistent across subgroups stratified by PD-L1 expression, stage of disease, or tumor mutational burden (TMB)[517]. A Phase 1 study of nivolumab combined with the immunostimulatory therapy bempegaldesleukin for immunotherapy-naive patients with NSCLC reported an ORR of 60% (3/5; 2 CRs) and mPFS of 18.0 months[518].

Nivolumab + Ipilimumab

Assay findings association

CD274 (PD-L1)
amplification

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, and ipilimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. The combination is FDA approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), and pleural mesothelioma. Furthermore, nivolumab is approved in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence for PD-L1 overexpression across various solid tumor types, alterations that lead to activation of CD274 may predict sensitivity to combination nivolumab and ipilimumab[31,73,180,519-520] .

SUPPORTING DATA

The Phase 3 CheckMate 227 study of nivolumab plus ipilimumab for patients with advanced non-small cell lung cancer (NSCLC) reported improved median OS relative to chemotherapy (17.1 vs. 13.9 months, HR=0.73) regardless of PD-L1 positivity, histology, tumor mutational burden (TMB) status, or brain metastases[41,521-522] , despite earlier analysis of this trial that suggested improved PFS only for patients with TMB ≥10 Muts/Mb (as measured by this assay)[27]. Similar results were observed in the Phase 3 CheckMate 9LA study, which reported significantly improved 2-year OS (38% vs. 26%), median PFS (6.7 months vs. 5.3 months), and ORR (38% vs. 25%) for patients treated with nivolumab plus ipilimumab in combination with chemotherapy when compared with patients treated with chemotherapy alone[523].

Pembrolizumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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 (TMB)-high (≥10 Muts/Mb), microsatellite instability-high (MSI-H), or mismatch repair-deficient (dMMR) solid tumors; as monotherapy for PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), cervical cancer, or gastric, esophageal, or gastroesophageal junction (GEJ) cancer; and in combination with chemotherapy for PD-L1-positive triple-negative breast cancer (TNBC) or cervical cancer. It is also approved in various treatment settings as monotherapy for patients with melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, classical Hodgkin lymphoma, or primary mediastinal large B-cell lymphoma, and in combination with chemotherapy or targeted therapy for NSCLC, HNSCC, esophageal or GEJ cancer, renal cell carcinoma, TNBC, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information. A voluntary withdrawal of the accelerated approval of pembrolizumab for the treatment of patients with recurrent advanced PD-L1-positive gastric or GEJ adenocarcinoma with disease progression on or after two or more prior lines of therapy has been initiated by the manufacturer.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to pembrolizumab. Treatment with pembrolizumab has resulted in a lasting CR in a patient with CD274-amplified DLBCL[524] and in a lasting PR in a patient with CD274-amplified cancer of unknown primary[71]. PD-L1 expression is associated with significantly prolonged median OS for patients with EGFR/ALK wildtype advanced NSCLC treated with pembrolizumab compared with chemotherapy[464,525-526] . One trial in patients with melanoma observed an improved objective response rate (51% vs. 6%) and PFS (12 vs. 3 months) for PD-L1 positive compared to PD-L1 negative tumors[462]. Furthermore, PD-L1 expression correlated positively with expression of PD-1 (on lymphocytes) and PD-L2, as well as with objective response to the anti-PD-1 antibody nivolumab in various advanced solid tumors[75].

SUPPORTING DATA

The superiority of pembrolizumab over platinum chemotherapy as first-line treatment for patients with PD-L1-positive non-small cell lung cancer (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)[525] and ≥50% (26.3 vs. 13.4 months, HR=0.62-0.69)[527], with estimated 5-year OS rates of 32% versus 16% in the KEYNOTE-024 study[527]. 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 PD-L1 expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[528]. 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 of 90-100% relative to those with TPS of 50-89% (not reached vs. 15.9 months, HR=0.39)[529]. 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)[530] or squamous (KEYNOTE-407)[531-532] NSCLC, regardless of PD-L1 or tumor mutational burden (TMB) status[40]. An exploratory analysis of KEYNOTE-189 demonstrated the superiority of the pembrolizumab combination therapy, regardless of blood TMB (bTMB) status[533]. 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 (+22%, p=0.011)[534]. 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[464]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single agent and in combination with chemotherapy, to treat patients with NSCLC and brain metastases[535-537] . Clinical activity has also been achieved with pembrolizumab in combination with the AXL inhibitor bemcentinib[538], the anti-CTLA-4 antibody ipilimumab[539], the anti-TIGIT antibody vibostolimab[540], the HDAC inhibitor vorinostat[541], the multikinase inhibitor lenvatinib[542], and the PARP inhibitor niraparib[543].

Tepotinib

Assay findings association

MET
exon 14 splice site (2888-1G>C), amplification

AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with metastatic non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[100,130,132,451-453], MET mutations associated with exon 14 skipping may predict sensitivity to selective MET inhibitors. On the basis of clinical data in non-small cell lung cancer[100,106-109,454], hepatocellular carcinoma[105], renal cell carcinoma[110], and gastric cancer[111], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

In the Phase 2 VISION study, tepotinib yielded an ORR of 45%, median duration of response (DOR) of 11 months, and median PFS of 8.9 months for patients with NSCLC and MET exon 14 skipping alterations, with similar ORRs observed for treatment-naïve and previously treated patients[130,453]. Among patients with brain metastases, tepotinib yielded an ORR of 57% (8/14)[544], median DOR of 9.5 months, and median PFS of 10.9 months[130]. The Phase 2 VISION study of tepotinib reported an ORR of 42% (10/24) and an mPFS of 4.2 months for patients with MET-amplified advanced non-small cell lung cancer, with responses observed in the first-, second-, and third-line settings[106]. Tepotinib has primarily been investigated in non-small cell lung cancer (NSCLC) and has demonstrated efficacy as a single agent for patients with MET amplification[106] and MET exon 14-skipping alterations[130,453]. Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[108-109]. A case study reported 1 PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC metastatic to the brain[131].

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

Avelumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as avelumab based on clinical evidence in multiple solid tumor types[64,188,439,501-504] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as avelumab. Although avelumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to the similar PD-L1-blocking antibody atezolizumab[64,188,439] .

SUPPORTING DATA

In the Phase 3 JAVELIN Lung 200 study for patients with advanced non-small cell lung cancer (NSCLC) previously treated with platinum therapy, avelumab did not improve median OS (mOS) when compared with docetaxel (11.4 vs. 10.6 months; HR=0.87) for patients with PD-L1 expression in ≥1% of tumor cells; a prespecified exploratory analysis at higher PD-L1 expression cutoffs showed improved mOS for PD-L1 ≥50% (13.6 vs. 9.2 months; HR=0.67) and ≥80% (17.1 vs. 9.3 months; HR=0.59)[545], and improved 2-year OS rates of 30% versus 21% (≥1% PD-L1), 36% versus 18% (≥50% PD-L1), and 40% versus 20% (≥80% PD-L1)[546]. A post-hoc analysis of this study suggested that a relatively high proportion of patients in the docetaxel arm received subsequent immune checkpoint inhibitor treatment, which may have confounded the outcomes of this study[547]. A Phase 1 study evaluating single-agent avelumab to treat patients with advanced NSCLC reported an ORR of 20%, median PFS (mPFS) of 4.0 months, and mOS of 14.1 months in the first-line setting[548]. A Phase 2 study of avelumab with axitinib to treat advanced NSCLC reported an ORR of 32% (13/41) and mPFS of 5.5 months; tumor reduction was observed for PD-L1-negative and -positive (≥1% PD-L1) samples[549]. A Phase 1b/2 study of avelumab combined with the anti-semaphorin 4D antibody pepinemab to treat advanced NSCLC reported an ORR of 24% (5/21) and DCR of 81% for immunotherapy-naive patients, and ORR of 6.9% (2/29) and DCR of 59% for patients who had disease progression on prior immunotherapy treatment[550]. A study of neoadjuvant avelumab plus chemotherapy to treat early-stage resectable NSCLC reported an ORR of 27% (4/15), which was not considered an enhancement over chemotherapy alone[551].

Cabozantinib

Assay findings association

MET
exon 14 splice site (2888-1G>C), amplification

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved as monotherapy to treat patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer (MTC), and differentiated thyroid cancer (DTC). It is also approved in combination with nivolumab to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[125,552] , as well as by extensive preclinical data[553-559] .

SUPPORTING DATA

Cabozantinib elicited a CR in a patient with lung adenocarcinoma harboring a MET amplification and a mutation affecting MET exon 14 splicing[125]. A Phase 2 randomized discontinuation trial of cabozantinib reported a 10.0% (6/60) ORR and a 58.3% (35/60) DCR, with median PFS of 4.2 months, for patients with genomically unselected, heavily pretreated NSCLC[560]. Patients with EGFR wild-type non-squamous NSCLC who had progressed after previous treatment experienced longer median PFS with cabozantinib alone or combined with erlotinib (4.3 and 4.7 months, HR=0.39 and 0.37, respectively) compared with single agent erlotinib (1.8 months) in a randomized Phase 2 trial[561]. A Phase 1 study of cabozantinib for advanced solid tumors reported an ORR of 20.0% (4/20; 4 PRs, all in EGFR-mutated tumors) and DCR of 100% (20/20) in the expansion cohort for Japanese patients with NSCLC[562].

Niraparib

Assay findings association

ATM
R337H

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[195-197,563] , colorectal cancer[199], breast cancer[199], gastric cancer[198], cholangiocarcinoma[201], and papillary renal cell carcinoma[200]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

In a Phase 1 study of niraparib treatment for patients with solid tumors, 2/2 patients with non-small cell lung cancer (NSCLC) achieved stable disease; 1/2 patients harbored a BRCA2 mutation[564]. In the Phase 2 JASPER study of niraparib in combination with pembrolizumab for patients with metastatic and/or locally advanced NSCLC, patients in the PD-L1 tumor proportion score (TPS) ≥50% and TPS 1-49% cohorts experienced ORRs of 56% (n=16, 2 CRs, 7 PRs) and 20% (n=20, 4 PRs), median PFSs of 8.4 months and 4.2 months, and median OSs of not estimable and 7.7 months, respectively[543]. Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[565]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[564]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[566].

Olaparib

Assay findings association

ATM
R337H

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[195-197,563] , colorectal cancer[199], breast cancer[199], gastric cancer[198], cholangiocarcinoma[201], and papillary renal cell carcinoma[200]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

In the Phase 2 PIPSeN study, maintenance treatment with olaparib did not significantly increase either median PFS (mPFS; 2.3 vs 2.1 months, HR=0.89, p=0.68) or median OS (mOS; 9.5 vs 14.1 months, HR=1.29, p=0.44) compared with placebo for patients with advanced non-small cell lung cancer (NSCLC) lacking EGFR, ALK, and ROS alterations[567o1942-o). In the Phase 2 GOAL study, the addition of olaparib to gefitinib did not significantly increase either mPFS (10.9 vs. 12.8 months, HR=1.38, p=0.12) or mOS (23.1 vs. 23.3 months, HR=0.82, p=0.345) for patients with EGFR-mutated NSCLC, unselected for other mutations; the ORR for patients treated with the combination (71%, 60/84) was similar to that of those treated with single-agent gefitinib (68%, 61/90)[568].

Rucaparib

Assay findings association

ATM
R337H

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[195-197,563] , colorectal cancer[199], breast cancer[199], gastric cancer[198], cholangiocarcinoma[201], and papillary renal cell carcinoma[200]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 study of rucaparib in advanced NSCLC closed due to futility; the reported ORR was 7% (n=59) for patients with BRCA-mutated or high genomic loss of heterozygosity[569]. Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[570]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[571]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[572]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[573]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[574]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[575]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[576]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[577].

Talazoparib

Assay findings association

ATM
R337H

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[195-197,563] , colorectal cancer[199], breast cancer[199], gastric cancer[198], cholangiocarcinoma[201], and papillary renal cell carcinoma[200]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 study of talazoparib in patients with squamous cell lung cancer harboring homologous recombination repair deficiency reported modest activity with an ORR of 11% (5/47), a DCR of 53% (25/47), a median PFS of 2.5 months and a median OS of 5.7 months[481].

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

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

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

GENE
ATM

ALTERATION
R337H

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or DNA-PKcs inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04380636

PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Lima (Peru), Arequipa (Peru), Antofagasta (Chile), Vina del Mar (Chile), Santiago (Chile), Temuco (Chile), Orizaba (Mexico), Florida, Tlalpan (Mexico)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Lima (Peru), Trujillo (Peru), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Buenos Aires (Argentina), Ciudad de Buenos Aires (Argentina), Berazategui (Argentina), Guatemala (Guatemala)

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Lima (Peru), Bellavista (Peru), Cuzco (Peru), Arequipa (Peru), Cali (Colombia), Medellin (Colombia), Bucaramanga (Colombia), La Rioja (Argentina), Barranquilla (Colombia), Ciudad de Buenos Aires (Argentina)

NCT02693535

PHASE 2

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

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

LOCATIONS: Florida, Georgia, South Carolina, Texas, Alabama, North Carolina

NCT04216316

PHASE 1/2

Testing the Addition of an Anti-cancer Drug, M6620, to the Usual Treatments (Carboplatin and Gemcitabine) and to Avelumab for Non-small Cell Lung Cancer

TARGETS
ATR, PD-1

LOCATIONS: Florida, North Carolina, Virginia, Missouri

NCT04768296

PHASE 2

Berzosertib + Topotecan in Relapsed Platinum-Resistant Small-Cell Lung Cancer (DDRiver SCLC 250)

TARGETS
TOP1, ATR

LOCATIONS: Bordeaux cedex (France), Texas, North Carolina, Saint-Herblain (France), Ohio, Missouri, Kansas, Indiana

NCT03221400

PHASE 1/2

PEN-866 in Patients With Advanced Solid Malignancies

TARGETS
PARP, HSP90

LOCATIONS: Florida, South Carolina, Tennessee, Arkansas, Virginia, Maryland, Oklahoma

NCT04991480

PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
PARP, Pol theta

LOCATIONS: Florida, Texas, Tennessee, Oklahoma

NCT04514497

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
ATR, TOP1

LOCATIONS: Florida, Tennessee, Oklahoma, Missouri, Connecticut, Arizona

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

GENE
CD274 (PD-L1)

ALTERATION
amplification

RATIONALE
CD274 (PD-L1) amplification or rearrangements that disrupt the 3' UTR may promote PD-1 signaling and inhibit the antitumor immune response. Antibodies that block the interaction of PD-L1 and PD-1 (alone or in combination with anti-CTLA-4) may therefore be beneficial to release the antitumor immune response. Furthermore, JAK2 inhibitors may be relevant, because they may reduce PD-L1 expression.

NCT03800134

PHASE 3

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

TARGETS
PD-L1

LOCATIONS: San Isidro (Peru), Lima (Peru), Bellavista (Peru), San Salvador de Jujuy (Argentina), Viña del Mar (Chile), Santiago (Chile), San José (Costa Rica), Rosario (Argentina), Pergamino (Argentina), Temuco (Chile)

NCT03735121

PHASE 3

A Study to Investigate the Pharmacokinetics, Efficacy, and Safety of Atezolizumab Subcutaneous in Patients With Stage IV Non-Small Cell Lung Cancer

TARGETS
PD-L1, VEGFA

LOCATIONS: Arequipa (Peru), Lima (Peru), Salta (Argentina), La Rioja (Argentina), Vina Del Mar (Chile), Recoleta (Chile), Temuco (Chile), Ijui (Brazil), Guatemala (Guatemala), Ciudad de Guatemala (Guatemala)

NCT04385368

PHASE 3

Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Lima (Peru), Bellavista (Peru), Trujillo (Peru), Rosario (Argentina), São José do Rio Preto (Brazil), Cipolletti (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Ciudad de Buenos Aires (Argentina), Caba (Argentina), Blumenau (Brazil)

NCT04380636

PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Lima (Peru), Arequipa (Peru), Antofagasta (Chile), Vina del Mar (Chile), Santiago (Chile), Temuco (Chile), Orizaba (Mexico), Florida, Tlalpan (Mexico)

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: San Isidro (Peru), Ijui (Brazil), Cdmx (Mexico), Mexico (Mexico), Florida, Monterrey (Mexico), Tennessee, Virginia

NCT04521621

PHASE 1/2

A Study of V937 in Combination With Pembrolizumab (MK-3475) in Participants With Advanced/ Metastatic Solid Tumors (V937-013)

TARGETS
PD-1

LOCATIONS: Lima (Peru), Taichung (Taiwan), New Jersey, Toronto (Canada), Montreal (Canada), Oregon, Porto (Portugal), Madrid (Spain), Barcelona (Spain), Villejuif (France)

NCT03976375

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Lenvatinib (E7080/MK-7902) vs. Docetaxel in Participants With Metastatic Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease (PD) After Platinum Doublet Chemotherapy and Immunotherapy (MK-7902-008/E7080-G000-316/LEAP-008)

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

LOCATIONS: Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Barranquilla (Colombia), Rosario (Argentina), Caba (Argentina), Buenos Aires (Argentina), Ponce (Puerto Rico)

NCT04738487

PHASE 3

Vibostolimab (MK-7684) With Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab (MK-3475) Monotherapy for Programmed Cell Death 1 Ligand 1 (PD-L1) Positive Metastatic Non-Small Cell Lung Cancer (MK-7684A-003)

TARGETS
TIGIT, PD-1

LOCATIONS: La Serena (Chile), Providencia (Chile), Talca (Chile), Temuco (Chile), Puerto Montt (Chile), Guatemala (Guatemala), Guatemala City (Guatemala), Oaxaca (Mexico), Merida (Mexico), Mexico city (Mexico)

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, PD-L1, CTLA-4

LOCATIONS: Vina del Mar (Chile), Santiago de Chile (Chile), Rio Cuarto (Argentina), Ijui (Brazil), Cuiudad Autonoma De Buenos Aires (Argentina), Buenos Aires (Argentina), Barretos (Brazil), Porto Alegre - Rs (Brazil), Blumenau (Brazil), Hato Rey (Puerto Rico)

NCT04513925

PHASE 3

A Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Participants With Locally Advanced, Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC)

TARGETS
TIGIT, PD-L1

LOCATIONS: Cordoba (Argentina), Sao Jose do Rio Preto (Brazil), Buenos Aires (Argentina), Ciudad Autonoma Buenos Aires (Argentina), Barretos (Brazil), Curitiba (Brazil), Porto Alegre (Brazil), Sao Paulo (Brazil), Florida, Fortaleza (Brazil)

GENE
CDK4

RATIONALE
CDK4 amplification may predict sensitivity to CDK4/6 inhibitors.

ALTERATION
amplification

NCT02693535

PHASE 2

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

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

LOCATIONS: Florida, Georgia, South Carolina, Texas, Alabama, North Carolina

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Florida, Louisiana, Texas, Mississippi, Georgia, North Carolina

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04553133

PHASE 1/2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS
CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Texas, Massachusetts, Michigan

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

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04557449

PHASE 1

Study to Test the Safety and Tolerability of PF-07220060 in Participants With Advance Solid Tumors

TARGETS
CDK4, Aromatase, ER

LOCATIONS: Texas, Tennessee, Connecticut, Massachusetts, Michigan

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

LOCATIONS: Bordeaux (France), Toulouse (France), Marseille (France), Lyon (France), Nice (France)

GENE
CDK6

ALTERATION
amplification

RATIONALE
Tumors with CDK6 amplification may be sensitive to CDK4/6 inhibitors.

NCT02693535

PHASE 2

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

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

LOCATIONS: Florida, Georgia, South Carolina, Texas, Alabama, North Carolina

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Florida, Louisiana, Texas, Mississippi, Georgia, North Carolina

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04553133

PHASE 1/2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS
CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Texas, Massachusetts, Michigan

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

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

LOCATIONS: Bordeaux (France), Toulouse (France), Marseille (France), Lyon (France), Nice (France)

NCT04594005

PHASE 1/2

CDK4/6 Tumor, Abemaciclib, Paclitaxel

TARGETS
CDK4, CDK6

LOCATIONS: Seoul (Korea, Republic of)

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

GENE
MDM2

ALTERATION
amplification

RATIONALE
Inhibitors of the MDM2-p53 interaction are being tested in clinical trials. Overexpression or amplification of MDM2 may increase sensitivity to these agents, but more data are required.

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Sao Paulo (Brazil), San Juan (Puerto Rico), Florida, Alabama, Texas, Georgia, South Carolina

NCT03611868

PHASE 1/2

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

TARGETS
MDM2, PD-1

LOCATIONS: Florida, Texas, Tennessee, Virginia, Arkansas, District of Columbia, Pennsylvania, Missouri

NCT03449381

PHASE 1

This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)

TARGETS
MDM2

LOCATIONS: Florida, Tennessee, New York, Connecticut, Ottawa (Canada), Barcelona (Spain), Leuven (Belgium), Tübingen (Germany), Berlin (Germany), Tokyo, Chuo-ku (Japan)

NCT03725436

PHASE 1

ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors

TARGETS
MDM2, MDM4

LOCATIONS: Texas

GENE
MET

ALTERATION
exon 14 splice site (2888-1G>C), amplification

RATIONALE
Activation of MET may lead to increased MET expression and activation and may therefore confer sensitivity to MET inhibitors.

NCT04427072

PHASE 3

Study of Capmatinib Efficacy in Comparison With Docetaxel in Previously Treated Participants With Non-small Cell Lung Cancer Harboring MET Exon 14 Skipping Mutation

TARGETS
MET

LOCATIONS: Barretos (Brazil), Sao Paulo (Brazil), Lisboa (Portugal), Matosinhos (Portugal), Porto (Portugal), La Coruna (Spain), Malaga (Spain), Oviedo (Spain), Madrid (Spain), Valencia (Spain)

NCT03906071

PHASE 3

Phase 3 Study of Sitravatinib Plus Nivolumab vs Docetaxel in Patients With Advanced Non-Squamous NSCLC

TARGETS
PD-1, AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB

LOCATIONS: Florida

NCT02693535

PHASE 2

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

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

LOCATIONS: Florida, Georgia, South Carolina, Texas, Alabama, North Carolina

NCT04310007

PHASE 2

Testing the Addition of the Pill Chemotherapy, Cabozantinib, to the Standard Immune Therapy Nivolumab Compared to Standard Chemotherapy for Non-small Cell Lung Cancer

TARGETS
MET, ROS1, RET, VEGFRs, PD-1

LOCATIONS: Florida, Louisiana, Georgia, South Carolina, Alabama

NCT03539536

PHASE 2

Study of Telisotuzumab Vedotin (ABBV-399) in Subjects With Previously Treated c-Met+ Non-Small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Florida, Alabama, Mississippi, Texas, Craiova (Romania), Tennessee

NCT03175224

PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Rio Piedras (Puerto Rico), Florida, Louisiana, South Carolina

NCT04077099

PHASE 1/2

REGN5093 in Patients With MET-Altered Advanced Non-Small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Bordeaux Cedex 9 (France), Montpellier (France), Florida, Texas, Alabama, Kentucky, District of Columbia, Pennsylvania, Missouri

NCT02795156

PHASE 2

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

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

LOCATIONS: Florida, Tennessee, Missouri, Wisconsin, Colorado

NCT03170960

PHASE 1/2

Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-L1, MET, ROS1, RET, VEGFRs

LOCATIONS: Florida, Louisiana, South Carolina, Texas, Georgia, Virginia

NCT02609776

PHASE 1

A Dose Escalation Study of JNJ-61186372 in Participants With Advanced Non-Small Cell Lung Cancer

TARGETS
MET, EGFR

LOCATIONS: Florida, Texas, Virginia, Maryland, Pennsylvania, Missouri, New York, Massachusetts, Michigan, Illinois

GENE
PDCD1LG2 (PD-L2)

ALTERATION
amplification

RATIONALE
PDCD1LG2 (PD-L2) amplification may promote PD-1 signaling and inhibit the anti-tumor immune response. Antibodies that block the interaction of PD-L2 and PD-1 may therefore be beneficial to release the anti-tumor immune response. Furthermore, JAK2 inhibitors may be relevant, because they may reduce PD-L2 expression.

NCT03800134

PHASE 3

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

TARGETS
PD-L1

LOCATIONS: San Isidro (Peru), Lima (Peru), Bellavista (Peru), San Salvador de Jujuy (Argentina), Viña del Mar (Chile), Santiago (Chile), San José (Costa Rica), Rosario (Argentina), Pergamino (Argentina), Temuco (Chile)

NCT03735121

PHASE 3

A Study to Investigate the Pharmacokinetics, Efficacy, and Safety of Atezolizumab Subcutaneous in Patients With Stage IV Non-Small Cell Lung Cancer

TARGETS
PD-L1, VEGFA

LOCATIONS: Arequipa (Peru), Lima (Peru), Salta (Argentina), La Rioja (Argentina), Vina Del Mar (Chile), Recoleta (Chile), Temuco (Chile), Ijui (Brazil), Guatemala (Guatemala), Ciudad de Guatemala (Guatemala)

NCT04385368

PHASE 3

Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Lima (Peru), Bellavista (Peru), Trujillo (Peru), Rosario (Argentina), São José do Rio Preto (Brazil), Cipolletti (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Ciudad de Buenos Aires (Argentina), Caba (Argentina), Blumenau (Brazil)

NCT04380636

PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Lima (Peru), Arequipa (Peru), Antofagasta (Chile), Vina del Mar (Chile), Santiago (Chile), Temuco (Chile), Orizaba (Mexico), Florida, Tlalpan (Mexico)

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: San Isidro (Peru), Ijui (Brazil), Cdmx (Mexico), Mexico (Mexico), Florida, Monterrey (Mexico), Tennessee, Virginia

NCT04521621

PHASE 1/2

A Study of V937 in Combination With Pembrolizumab (MK-3475) in Participants With Advanced/Metastatic Solid Tumors (V937-013)

TARGETS
PD-1

LOCATIONS: Lima (Peru), Taichung (Taiwan), New Jersey, Toronto (Canada), Montreal (Canada), Oregon, Porto (Portugal), Madrid (Spain), Barcelona (Spain), Villejuif (France)

NCT03976375

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Lenvatinib (E7080/MK-7902) vs. Docetaxel in Participants With Metastatic Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease (PD) After Platinum Doublet Chemotherapy and Immunotherapy (MK-7902-008/E7080-G000-316/LEAP-008)

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

LOCATIONS: Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Barranquilla (Colombia), Rosario (Argentina), Caba (Argentina), Buenos Aires (Argentina), Ponce (Puerto Rico)

NCT04738487

PHASE 3

Vibostolimab (MK-7684) With Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab (MK-3475) Monotherapy for Programmed Cell Death 1 Ligand 1 (PD-L1) Positive Metastatic Non-Small Cell Lung Cancer (MK-7684A-003)

TARGETS
TIGIT, PD-1

LOCATIONS: La Serena (Chile), Providencia (Chile), Talca (Chile), Temuco (Chile), Puerto Montt (Chile), Guatemala (Guatemala), Guatemala City (Guatemala), Oaxaca (Mexico), Merida (Mexico), Mexico city (Mexico)

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, PD-L1, CTLA-4

LOCATIONS: Vina del Mar (Chile), Santiago de Chile (Chile), Rio Cuarto (Argentina), Ijui (Brazil), Cuiudad Autonoma De Buenos Aires (Argentina), Buenos Aires (Argentina), Barretos (Brazil), Porto Alegre - Rs (Brazil), Blumenau (Brazil), Hato Rey (Puerto Rico)

NCT04513925

PHASE 3

A Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Participants With Locally Advanced, Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC)

TARGETS
TIGIT, PD-L1

LOCATIONS: Cordoba (Argentina), Sao Jose do Rio Preto (Brazil), Buenos Aires (Argentina), Ciudad Autonoma Buenos Aires (Argentina), Barretos (Brazil), Curitiba (Brazil), Porto Alegre (Brazil), Sao Paulo (Brazil), Florida, Fortaleza (Brazil)

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.

BCL6
amplification

ERBB2
E1114K

GSK3B
E97K

KDM5A
R85T

MAP2K2 (MEK2)
D249H

MLL2
amplification

MYC
V20F

NFE2L2
P578_N590del

NTRK1
G18E

SDHA
amplification

TEK
V676I

TET2
V636L

TSC1
K587R

WT1
G38C

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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 is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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 fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of 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. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

MR Suite Version 6.0.0

The median exon coverage for this sample is 489x

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Warth A, et al. Virchows Arch. (2016) pmid: 26637197
7. Ninomiya H, et al. Br. J. Cancer (2006) pmid: 16641899
8. Vanderwalde A, et al. Cancer Med (2018) pmid: 29436178
9. Zang YS, et al. Cancer Med (2019) pmid: 31270941
10. Dudley JC, et al. Clin. Cancer Res. (2016) pmid: 26880610
11. Takamochi K, et al. Lung Cancer (2017) pmid: 28676214
12. Pylkkänen L, et al. Environ. Mol. Mutagen. (1997) pmid: 9329646
13. Gonzalez R, et al. Ann. Oncol. (2000) pmid: 11061602
14. Chen XQ, et al. Nat. Med. (1996) pmid: 8782463
15. Merlo A, et al. Cancer Res. (1994) pmid: 8174113
16. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
17. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
18. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
19. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
20. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
21. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
22. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
23. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
24. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
25. Cristescu R, et al. Science (2018) pmid: 30309915
26. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
27. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
28. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
29. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
30. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
31. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
32. Rizvi NA, et al. Science (2015) pmid: 25765070
33. Colli LM, et al. Cancer Res. (2016) pmid: 27197178
34. Wang VE, et al. J Immunother Cancer (2017) pmid: 28923100
35. Carbone DP, et al. N. Engl. J. Med. (2017) pmid: 28636851
36. Rizvi H, et al. J. Clin. Oncol. (2018) pmid: 29337640
37. Forde PM, et al. N. Engl. J. Med. (2018) pmid: 29658848
38. Miao D, et al. Nat. Genet. (2018) pmid: 30150660
39. Chae YK, et al. Clin Lung Cancer (2019) pmid: 30425022
40. Paz-Ares et al., 2019; ESMO Abstract LBA80
41. Hellmann MD, et al. N. Engl. J. Med. (2019) pmid: 31562796
42. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
43. Spigel et al., 2016; ASCO Abstract 9017
44. Xiao D, et al. Oncotarget (2016) pmid: 27009843
45. Shim HS, et al. J Thorac Oncol (2015) pmid: 26200269
46. Govindan R, et al. Cell (2012) pmid: 22980976
47. Ding L, et al. Nature (2008) pmid: 18948947
48. Imielinski M, et al. Cell (2012) pmid: 22980975
49. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
50. Stein et al., 2019; DOI: 10.1200/PO.18.00376
51. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
52. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
53. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
54. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
55. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
56. Johnson BE, et al. Science (2014) pmid: 24336570
57. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
58. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
59. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
60. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
61. Nature (2012) pmid: 22810696
62. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
63. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
64. Fehrenbacher L, et al. Lancet (2016) pmid: 26970723
65. Herbst RS, et al. Nature (2014) pmid: 25428504
66. Massard C, et al. J. Clin. Oncol. (2016) pmid: 27269937
67. Bais et al., 2017; AACR Abstract 3720/5
68. Garassino et al., 2016; IASLC Abstract PLO4a.03
69. Segal et al., 2015; ASCO Abstract 3011
70. Rebelatto et al., 2015; ASCO Abstract 8033
71. Gröschel S, et al. Cold Spring Harb Mol Case Stud (2016) pmid: 27900363
72. Bauman WA, et al. Am J Med (1988) pmid: 3291612
73. Motzer RJ, et al. N. Engl. J. Med. (2018) pmid: 29562145
74. Ansell SM, et al. N. Engl. J. Med. (2015) pmid: 25482239
75. Taube JM, et al. Clin. Cancer Res. (2014) pmid: 24714771
76. Sharma et al., 2018; AACR abstract CT178
77. Paz-Ares L, et al. J Thorac Oncol (2020) pmid: 32173464
78. Green MR, et al. Blood (2010) pmid: 20628145
79. Derenzini E, et al. Blood Cancer J (2011) pmid: 22829094
80. Nature (2014) pmid: 25079552
81. Nature (2012) pmid: 22960745
82. Mu CY, et al. Med. Oncol. (2011) pmid: 20373055
83. Hamanishi J, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17360651
84. Chen YB, et al. Tumori (2012) pmid: 23389362
85. Keir ME, et al. Annu. Rev. Immunol. (2008) pmid: 18173375
86. Butte MJ, et al. Immunity (2007) pmid: 17629517
87. Benson DM, et al. Blood (2010) pmid: 20460501
88. Iwai Y, et al. Proc. Natl. Acad. Sci. U.S.A. (2002) pmid: 12218188
89. Liu J, et al. Blood (2007) pmid: 17363736
90. Huang RSP, et al. Mod Pathol (2021) pmid: 32884129
91. Nature (2014) pmid: 25079317
92. George J, et al. Clin. Cancer Res. (2017) pmid: 27620277
93. Ou SH, et al. J Thorac Oncol (2011) pmid: 21623265
94. Schwab R, et al. Lung Cancer (2014) pmid: 24192513
95. Le X, et al. Clin Lung Cancer (2015) pmid: 25922291
96. Schrock AB, et al. J Thorac Oncol (2017) pmid: 28315738
97. Lennerz JK, et al. J. Clin. Oncol. (2011) pmid: 22042947
98. Chi AS, et al. J. Clin. Oncol. (2012) pmid: 22162573
99. Palma NA, et al. Case Rep Oncol (2014) pmid: 25232318
100. Schuler et al., 2016; ASCO Abstract 9067
101. Wu et al., 2018; WCLC Abstract P1.01-97
102. Wu YL, et al. J. Clin. Oncol. (2018) pmid: 30156984
103. Gainor JF, et al. J Thorac Oncol (2020) pmid: 31864558
104. Gautschi O, et al. J Thorac Oncol (2020) pmid: 31864554
105. Faivre et al., 2021; ASCO GI Abstract 329
106. Le et al., 2021; ASCO Abstract 9021
107. Yang et al., 2019; AACR Abstract CT193
108. Park et al., 2019; ESMO Abstract 477O
109. Wu et al., 2019; IASLC Abstract MA09.09
110. Gan HK, et al. Clin. Cancer Res. (2019) pmid: 30952639
111. Lee J, et al. Cancer Discov (2019) pmid: 31315834
112. Kim ST, et al. Transl Oncol (2019) pmid: 30695737
113. Kwak et al., 2015; ASCO GI Abstract 01
114. Spigel DR, et al. J. Clin. Oncol. (2013) pmid: 24101053
115. Catenacci DV, et al. Cancer Discov (2011) pmid: 22389872
116. Harding JJ, et al. Clin. Cancer Res. (2019) pmid: 31142504
117. Strickler JH, et al. J. Clin. Oncol. (2018) pmid: 30285518
118. Camidge et al., 2021; AACR Abstract CT179
119. Choueiri TK, et al. J. Clin. Oncol. (2013) pmid: 23213094
120. Diamond JR, et al. J. Clin. Oncol. (2013) pmid: 23610116
121. Stein MN, et al. Eur. Urol. (2015) pmid: 25457019
122. Choueiri TK, et al. JAMA Oncol (2020) pmid: 32469384
123. Frampton GM, et al. Cancer Discov (2015) pmid: 25971938
124. Engstrom LD, et al. Clin. Cancer Res. (2017) pmid: 28765324
125. Paik PK, et al. Cancer Discov (2015) pmid: 25971939
126. Jenkins RW, et al. Clin Lung Cancer (2015) pmid: 25769807
127. Waqar SN, et al. J Thorac Oncol (2015) pmid: 25898962
128. Mendenhall MA, et al. J Thorac Oncol (2015) pmid: 25898965
129. Awad et al., 2017; ASCO Abstract 8511
130. Paik PK, et al. N. Engl. J. Med. (2020) pmid: 32469185
131. Blanc-Durand F, et al. Oncologist (2020) pmid: 32716573
132. Lu et al., 2020; ASCO Abstract 9519
133. Yang et al., 2020; AACR Abstract CT127
134. Lu et al., 2019; AACR Abstract CT031
135. Le et al., 2020; AACR Abstract 3385
136. Dziadziuszko R, et al. J Thorac Oncol (2012) pmid: 22237262
137. Murray S, et al. J. Exp. Clin. Cancer Res. (2012) pmid: 22992338
138. Xia N, et al. Exp. Lung Res. (2013) pmid: 23919423
139. Nakamura Y, et al. Cancer Sci. (2007) pmid: 17459054
140. Park S, et al. Histol. Histopathol. (2012) pmid: 22207554
141. Cappuzzo F, et al. J. Clin. Oncol. (2009) pmid: 19255323
142. Zucali PA, et al. Ann. Oncol. (2008) pmid: 18467317
143. An SJ, et al. PLoS ONE (2012) pmid: 22768234
144. Yang JJ, et al. Lung Cancer (2013) pmid: 23079155
145. Chen YT, et al. J Thorac Oncol (2011) pmid: 22052229
146. Kanteti R, et al. J. Environ. Pathol. Toxicol. Oncol. (2009) pmid: 19817696
147. To C, et al. Exp. Cell Res. (2002) pmid: 11795945
148. Tsuta K, et al. J Thorac Oncol (2012) pmid: 22198430
149. Tanaka A, et al. Lung Cancer (2012) pmid: 21733594
150. Tong JH, et al. Clin. Cancer Res. (2016) pmid: 26847053
151. Lee GD, et al. J Thorac Oncol (2017) pmid: 28502721
152. Gow CH, et al. Lung Cancer (2017) pmid: 28024701
153. J. Clin. Oncol. (2011) pmid: 22042966
154. Jung KH, et al. Arch. Pharm. Res. (2012) pmid: 22553051
155. Gao J, et al. Sci Signal (2013) pmid: 23550210
156. Ang CS, et al. Anticancer Res. (2013) pmid: 23898085
157. Abou-Bakr AA, et al. Gulf J Oncolog (2013) pmid: 23996864
158. Ho JC, et al. Semin Respir Crit Care Med (2013) pmid:

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

24258573
159. Madoz-Gúrpide J, et al. J Transl Med (2015) pmid: 26319934
160. Ali SM, et al. Oncologist (2015) pmid: 25882375
161. Kwak EL, et al. Cancer Discov (2015) pmid: 26432108
162. Kong-Beltran M, et al. Cancer Res. (2006) pmid: 16397241
163. Onozato R, et al. J Thorac Oncol (2009) pmid: 19096300
164. Okuda K, et al. Cancer Sci. (2008) pmid: 19037978
165. Awad MM, et al. J. Clin. Oncol. (2016) pmid: 26729443
166. Gray MJ, et al. Am. J. Hum. Genet. (2015) pmid: 26637977
167. Peschard P, et al. J. Biol. Chem. (2004) pmid: 15123609
168. Lee JM, et al. Oncogene (2014) pmid: 23208509
169. Lee JH, et al. Exp. Mol. Med. (2006) pmid: 17079873
170. Togashi Y, et al. Lung Cancer (2015) pmid: 26547802
171. Peschard P, et al. Mol. Cell (2001) pmid: 11741535
172. Abella JV, et al. Mol. Cell. Biol. (2005) pmid: 16227611
173. Drilon et al., 2018; WCLC Abstract OA12.02
174. Felip et al., 2018; WCLC Abstract OA12.01
175. Wolf et al., 2018; ESMO Abstract LBA52
176. Moro-Sibilot et al., 2018; WCLC Abstract OA12.03
177. Berry ZS, et al. JAMA (1993) pmid: 8315738
178. Robert C, et al. N. Engl. J. Med. (2015) pmid: 25399552
179. Weber JS, et al. Lancet Oncol. (2015) pmid: 25795410
180. Larkin J, et al. N. Engl. J. Med. (2015) pmid: 26027431
181. Postow MA, et al. N. Engl. J. Med. (2015) pmid: 25891304
182. Topalian SL, et al. J. Clin. Oncol. (2014) pmid: 24590637
183. Brahmer J, et al. N. Engl. J. Med. (2015) pmid: 26028407
184. Borghaei H, et al. N. Engl. J. Med. (2015) pmid: 26412456
185. Rizvi NA, et al. Lancet Oncol. (2015) pmid: 25704439
186. Motzer RJ, et al. N. Engl. J. Med. (2015) pmid: 26406148
187. Ansell et al., 2015; ASH Abstract 583
188. Schmid et al., 2016; ASCO Abstract 11506
189. Verstovsek S, et al. Br. J. Haematol. (2013) pmid: 23480528
190. Zhang Y, et al. Onco Targets Ther (2014) pmid: 24748806
191. Kim MY, et al. Lung Cancer (2015) pmid: 25662388
192. Twa DD, et al. Blood (2014) pmid: 24497532
193. Shi M, et al. Am. J. Surg. Pathol. (2014) pmid: 25025450
194. Michels J, et al. Oncogene (2014) pmid: 24037533
195. Mateo J, et al. N. Engl. J. Med. (2015) pmid: 26510020
196. Mateo J, et al. Lancet Oncol. (2019) pmid: 31806540
197. Abida W, et al. Clin. Cancer Res. (2020) pmid: 32086346
198. Bang YJ, et al. J. Clin. Oncol. (2015) pmid: 26282658
199. Gruber et al., 2019; ASCO Abstract 3006
200. Olson D, et al. Clin Genitourin Cancer (2016) pmid: 27079472
201. Piha-Paul et al., 2018; AACR-NCI-EORTC Abstract A096
202. Weston VJ, et al. Blood (2010) pmid: 20739657
203. Williamson CT, et al. Mol. Cancer Ther. (2010) pmid: 20124459
204. Gilardini Montani MS, et al. J. Exp. Clin. Cancer Res. (2013) pmid: 24252502
205. Bryant HE, et al. Nucleic Acids Res. (2006) pmid: 16556909
206. Ihnen M, et al. Mol. Cancer Ther. (2013) pmid: 23729402
207. Williamson CT, et al. EMBO Mol Med (2012) pmid: 22416035
208. Kubota E, et al. Cell Cycle (2014) pmid: 24841718
209. Huehls AM, et al. Mol. Pharmacol. (2012) pmid: 22833573
210. O'Carrigan et al., 2016; ASCO Abstract 2504
211. Yap TA, et al. Cancer Discov (2021) pmid: 32988960
212. Menezes DL, et al. Mol. Cancer Res. (2015) pmid: 25232030
213. Vendetti FP, et al. Oncotarget (2015) pmid: 26517239
214. Min A, et al. Mol. Cancer Ther. (2017) pmid: 28138034
215. Kwok M, et al. Blood (2016) pmid: 26563132
216. Riabinska A, et al. Sci Transl Med (2013) pmid: 23761041
217. Pierceall WE, et al. Ann. Oncol. (2012) pmid: 22269178
218. Shiloh Y, et al. Nat. Rev. Mol. Cell Biol. (2013) pmid: 23847781
219. Cremona CA, et al. Oncogene (2014) pmid: 23851492
220. van Os NJ, et al. Clin Genet (2016) pmid: 26662178
221. Rothblum-Oviatt C, et al. Orphanet J Rare Dis (2016) pmid: 27884168
222. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
223. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
224. Xie M, et al. Nat. Med. (2014) pmid: 25326804
225. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
226. Severson EA, et al. Blood (2018) pmid: 29678827
227. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
228. Chabon JJ, et al. Nature (2020) pmid: 32269342
229. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
230. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
231. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
232. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
233. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
234. Dickson et al., 2019; ASCO Abstract 11004
235. Dickson MA, et al. JAMA Oncol (2016) pmid: 27124835
236. Peguero et al., 2016; ASCO Abstract 2528
237. Campbell JD, et al. Nat. Genet. (2016) pmid: 27158780
238. Wikman H, et al. Genes Chromosomes Cancer (2005) pmid: 15543620
239. Borczuk AC, et al. Am. J. Pathol. (2003) pmid: 14578194
240. Wu A, et al. J Transl Med (2011) pmid: 21477379
241. Puyol M, et al. Cancer Cell (2010) pmid: 20609353
242. Choi YJ, et al. Oncogene (2014) pmid: 23644662
243. Cell (1995) pmid: 7736585
244. Musgrove EA, et al. Nat. Rev. Cancer (2011) pmid: 21734724
245. Rao SK, et al. J. Neurooncol. (2010) pmid: 19609742
246. Chung L, et al. Am. J. Surg. Pathol. (2009) pmid: 19574885
247. Ragazzini P, et al. Histol. Histopathol. (2004) pmid: 15024701
248. Dujardin F, et al. Mod. Pathol. (2011) pmid: 21336260
249. Zhang K, et al. Cancer Res. (2013) pmid: 23393200
250. Horvai AE, et al. Mod. Pathol. (2009) pmid: 19734852
251. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
252. Turner NC, et al. N. Engl. J. Med. (2015) pmid: 26030518
253. Konecny et al., 2016; ASCO Abstract 5557
254. Zhao X, et al. Cancer Res. (2005) pmid: 15994928
255. Salim H, et al. Genes Chromosomes Cancer (2013) pmid: 23929716
256. Igarashi K, et al. Br. J. Cancer (1999) pmid: 10574260
257. Meyerson M, et al. Mol. Cell. Biol. (1994) pmid: 8114739
258. Grossel MJ, et al. J. Cell. Biochem. (2006) pmid: 16294322
259. Ismail A, et al. Clin. Cancer Res. (2011) pmid: 21593195
260. van Dekken H, et al. Cancer Genet. Cytogenet. (2009) pmid: 19167610
261. Cheok CF, et al. Nat Rev Clin Oncol (2011) pmid: 20975744
262. Ohnstad HO, et al. Cancer (2013) pmid: 23165797
263. Gamble LD, et al. Oncogene (2012) pmid: 21725357
264. Zhang et al., 2019; ASCO Abstract 3124
265. Rasco et al., 2019; ASCO Abstract 3126
266. Tolcher et al., 2021; ASCO Abstract 2506
267. Martinelli et al., 2016; EHA21 Abstract S504
268. Daver et al., 2018; ASH Abstract 767
269. Mascarenhas et al., 2019; ASH Abstract 134
270. Shustov et al., 2018; ASH Abstract 1623
271. Sallman et al., 2018; ASH Abstract 4066
272. Meric-Bernstam et al., 2017; ASCO Abstract 2505
273. Higashiyama M, et al. Br. J. Cancer (1997) pmid: 9155050
274. Marchetti A, et al. Diagn. Mol. Pathol. (1995) pmid: 7551299
275. Dworakowska D, et al. Lung Cancer (2004) pmid: 15165086
276. Onel K, et al. Mol. Cancer Res. (2004) pmid: 14757840
277. Ren YW, et al. Asian Pac. J. Cancer Prev. (2013) pmid: 24175836
278. Sdek P, et al. Mol. Cell (2005) pmid: 16337594
279. Brady M, et al. Mol. Cell. Biol. (2005) pmid: 15632057
280. Li M, et al. Mol. Cell (2004) pmid: 15053880
281. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
282. Cordon-Cardo C, et al. Cancer Res. (1994) pmid: 8306343
283. Beroukhim R, et al. Nature (2010) pmid: 20164920
284. Kato S, et al. Clin. Cancer Res. (2017) pmid: 28351930
285. Singavi et al., 2017; ESMO Abstract 1140PD
286. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
287. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
288. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
289. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
290. Elvin JA, et al. Oncologist (2017) pmid: 28283584
291. Gao J, et al. Curr Oncol (2015) pmid: 26715889
292. Gopalan et al., 2014; ASCO Abstract 8077
293. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
294. Johnson DB, et al. Oncologist (2014) pmid: 24797823
295. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
296. Doxtader EE, et al. Hum. Pathol. (2012) pmid: 21840041
297. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
298. Kratzke RA, et al. Cancer Res. (1996) pmid: 8758904
299. Lee JU, et al. Tuberc Respir Dis (Seoul) (2012) pmid: 23101020
300. Cortot AB, et al. Clin Lung Cancer (2014) pmid: 24169260
301. Mounawar M, et al. Cancer Res. (2007) pmid: 17575133
302. Kawabuchi B, et al. Int. J. Cancer (1999) pmid: 9988232
303. Xing XB, et al. PLoS ONE (2013) pmid: 23805242
304. Lou-Qian Z, et al. PLoS ONE (2013) pmid: 23372805
305. Quelle DE, et al. Cell (1995) pmid: 8521522
306. Mutat. Res. (2005) pmid: 15878778
307. Oncogene (1999) pmid: 10498883
308. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
309. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
310. Ruas M, et al. Oncogene (1999) pmid: 10498896
311. Jones R, et al. Cancer Res. (2007) pmid: 17909018

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

312. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
313. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
314. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
315. Gombart AF, et al. Leukemia (1997) pmid: 9324288
316. Yang R, et al. Cancer Res. (1995) pmid: 7780957
317. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
318. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
319. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
320. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
321. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
322. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
323. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
324. Koh J, et al. Nature (1995) pmid: 7777061
325. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
326. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
327. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
328. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
329. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
330. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
331. Rutter JL, et al. Oncogene (2003) pmid: 12853981
332. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
333. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
334. Zhang Y, et al. Cell (1998) pmid: 9529249
335. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
336. Adv Exp Med Biol (2010) pmid: 20687502
337. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
338. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
339. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
340. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
341. Kaufman DK, et al. Neurology (1993) pmid: 8414022
342. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
343. Chan AK, et al. Clin Neuropathol () pmid: 28699883
344. Kertesz N, et al. Blood (2006) pmid: 16322467
345. Shi S, et al. J Pharm Sci (2012) pmid: 22411527
346. Li X, et al. PLoS ONE (2014) pmid: 25148033
347. Liu R, et al. BMC Cancer (2013) pmid: 23721559
348. Bhatia S, et al. Sci Rep (2016) pmid: 27941840
349. Scehnet JS, et al. Blood (2009) pmid: 18836096
350. Ferguson BD, et al. Sci Rep (2015) pmid: 26073592
351. Werner TL, et al. Invest New Drugs (2015) pmid: 26365907
352. Pietanza MC, et al. J Thorac Oncol (2012) pmid: 22011666
353. Pietanza MC, et al. J Thorac Oncol (2012) pmid: 22722787
354. Sinha UK, et al. Arch. Otolaryngol. Head Neck Surg. (2006) pmid: 17043250
355. Masood R, et al. Int. J. Cancer (2006) pmid: 16615113
356. Ferguson BD, et al. Growth Factors (2014) pmid: 25391996
357. Yavrouian EJ, et al. Arch. Otolaryngol. Head Neck Surg. (2008) pmid: 18794445
358. Liersch-Löhn B, et al. Int. J. Cancer (2016) pmid: 26414866
359. Hu F, et al. Tumour Biol. (2014) pmid: 24771266
360. Hasina R, et al. Cancer Res. (2013) pmid: 23100466
361. Li M, et al. Dig. Dis. Sci. (2011) pmid: 20686847
362. Yin J, et al. Anticancer Res. (2017) pmid: 28739744
363. Stephenson SA, et al. BMC Mol. Biol. (2001) pmid: 11801186
364. Liu W, et al. Cancer (2002) pmid: 11920461
365. McCall JL, et al. Mol. Cell. Biol. (2016) pmid: 27273865
366. Stremitzer S, et al. Mol. Cancer Ther. (2016) pmid: 27535973
367. Lv J, et al. Exp. Mol. Pathol. (2016) pmid: 27072105
368. Guijarro-Muñoz I, et al. Med. Oncol. (2013) pmid: 23579861
369. Kumar SR, et al. Cancer Res. (2009) pmid: 19366806
370. Wu Q, et al. Pathol. Oncol. Res. (2004) pmid: 15029258
371. Berclaz G, et al. Oncol. Rep. () pmid: 12168060
372. Brantley-Sieders DM, et al. PLoS ONE (2011) pmid: 21935409
373. Huang G, et al. Int J Clin Exp Pathol (2015) pmid: 26191333
374. Pradeep S, et al. Cancer Cell (2015) pmid: 26481148
375. Alam SM, et al. Br. J. Cancer (2008) pmid: 18231102
376. Kumar SR, et al. Br. J. Cancer (2007) pmid: 17353927
377. Takai N, et al. Oncol. Rep. () pmid: 11295082
378. Dong LD, et al. Oncol Lett (2017) pmid: 28454369
379. Berclaz G, et al. Ann. Oncol. (2003) pmid: 12562648
380. Sharma GK, et al. Head Neck (2015) pmid: 24634162
381. Giaginis C, et al. Pathol. Oncol. Res. (2016) pmid: 26220827
382. Xuqing W, et al. Tumour Biol. (2012) pmid: 22528941
383. Ferguson BD, et al. PLoS ONE (2013) pmid: 23844053
384. Zheng MF, et al. Mol Med Rep (2012) pmid: 22684742
385. Chen T, et al. Tumour Biol. (2013) pmid: 23138393
386. Tu Y, et al. Clin Transl Oncol (2012) pmid: 22374425
387. Li M, et al. Mol. Biol. Rep. (2013) pmid: 23079712
388. Xia G, et al. Cancer Res. (2005) pmid: 15930280
389. Alam SM, et al. Gynecol. Oncol. (2009) pmid: 19356789
390. Ozgür E, et al. Urol. Oncol. () pmid: 19272799
391. Pierscianek D, et al. Neuropathology (2017) pmid: 27388534
392. Pierscianek D, et al. Brain Tumor Pathol (2016) pmid: 26951238
393. Becerikli M, et al. Int. J. Cancer (2015) pmid: 25274141
394. Xia G, et al. Clin. Cancer Res. (2005) pmid: 15958611
395. Noren NK, et al. Cancer Res. (2007) pmid: 17483308
396. Cell (2008) pmid: 18394988
397. Salvucci O, et al. Adv. Cancer Res. (2012) pmid: 22588055
398. Pitulescu ME, et al. Genes Dev. (2010) pmid: 21078817
399. Nat. Rev. Cancer (2010) pmid: 20179713
400. Boberg DR, et al. Chem. Biol. Interact. (2013) pmid: 23063927
401. Cromer A, et al. Oncogene (2004) pmid: 14676830
402. Black LE, et al. Am. J. Pathol. (2019) pmid: 31351986
403. Baselga J, et al. Nat. Rev. Cancer (2009) pmid: 19536107
404. Jaiswal BS, et al. Cancer Cell (2013) pmid: 23680147
405. Jura N, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 20007378
406. Choudhury NJ, et al. J. Clin. Oncol. (2016) pmid: 27044931
407. Verlingue L, et al. Eur. J. Cancer (2018) pmid: 29413684
408. Bidard FC, et al. Ann. Oncol. (2015) pmid: 25953157
409. Umelo I, et al. Oncotarget (2016) pmid: 26689995
410. Mishra R, et al. Oncotarget (2018) pmid: 29963236
411. Perez EA, et al. BMC Cancer (2019) pmid: 31146717
412. Baselga J, et al. J. Clin. Oncol. (2014) pmid: 25332247
413. Kim SB, et al. Int. J. Cancer (2016) pmid: 27428671
414. Baselga J, et al. Clin. Cancer Res. (2016) pmid: 26920887
415. Shah MA, et al. Gastric Cancer (2019) pmid: 30706247
416. Kurzeder C, et al. J. Clin. Oncol. (2016) pmid: 27269942
417. Cohen EEW, et al. Ann. Oncol. (2017) pmid: 28961833
418. LaBonte MJ, et al. Mol. Cancer Ther. (2016) pmid: 27325685
419. Nishimura R, et al. Oncology (2017) pmid: 28478451
420. Duchnowska R, et al. Oncotarget (2017) pmid: 29262628
421. Fabi A, et al. Expert Opin Pharmacother (2013) pmid: 23472669
422. Reinmuth N, et al. Eur. Respir. J. (2000) pmid: 11153605
423. Müller-Tidow C, et al. Cancer Res. (2005) pmid: 15753374
424. Bellezza G, et al. Virchows Arch. (2013) pmid: 24013863
425. Skrzypski M, et al. Clin Lung Cancer (2013) pmid: 23870818
426. Sheng Q, et al. Br. J. Cancer (2011) pmid: 21364581
427. Sassen A, et al. Breast Cancer Res. (2008) pmid: 18182100
428. Looyenga BD, et al. PLoS ONE (2012) pmid: 22319590
429. Zhao M, et al. Lung Cancer (2011) pmid: 21333372
430. Jatiani SS, et al. Genes Cancer (2010) pmid: 21442038
431. Chase A, et al. Haematologica (2013) pmid: 22875628
432. Stephens PJ, et al. J. Clin. Invest. (2013) pmid: 23778141
433. Rossi D, et al. J. Exp. Med. (2012) pmid: 22891273
434. Shi Y, et al. Genes Dev. (2001) pmid: 11331609
435. Ariyoshi M, et al. Genes Dev. (2003) pmid: 12897056
436. Kuroda K, et al. Immunity (2003) pmid: 12594956
437. Oswald F, et al. EMBO J. (2002) pmid: 12374742
438. Kopan R, et al. Cell (2009) pmid: 19379690
439. Herbst RS, et al. Clin. Cancer Res. (2015) pmid: 25680375
440. Jotte R, et al. J Thorac Oncol (2020) pmid: 32302702
441. Socinski MA, et al. N. Engl. J. Med. (2018) pmid: 29863955
442. West H, et al. Lancet Oncol. (2019) pmid: 31122901
443. Barlesi et al., 2018; ESMO Abstract LBA54
444. Herbst RS, et al. N Engl J Med (2020) pmid: 32997907
445. Rittmeyer A, et al. Lancet (2017) pmid: 27979383
446. Smith et al., 2016; ASCO Abstract 9028
447. Pietras et al., 2018; WCLC Abstract P1.04-3
448. Nie et al., 2020; WCLC Abstract OA07.03
449. Felip E, et al. Lancet (2021) pmid: 34555333
450. Rodriguez-Abreu et al., 2020; ASCO Abstract 9503
451. Wolf et al., 2019; ASCO Abstract 9004
452. Riedel et al., 2019; ASCO abstract 9030
453. Mazieres et al., 2020; ESMO Abstract 1283P
454. Wu et al., 2018; WLCL Abstract P1.01-97
455. Wolf J, et al. N Engl J Med (2020) pmid: 32877583
456. Schuler M, et al. Ann. Oncol. (2020) pmid: 32240796
457. Wolf et al., 2020; ESMO Abstract 1346P
458. Wolf et al., 2020; ASCO Abstract 9509
459. van den Bent M, et al. J. Neurooncol. (2020) pmid: 31776899
460. Bang YJ, et al. Cancer Sci. (2020) pmid: 31778267
461. Esaki T, et al. Cancer Sci. (2019) pmid: 30724423
462. Kefford et al., 2014; ASCO Abstract 3005
463. Garon EB, et al. N. Engl. J. Med. (2015) pmid: 25891174
464. Herbst RS, et al. Lancet (2016) pmid: 26712084
465. Bellone S, et al. Clin. Cancer Res. (2018) pmid: 29351920
466. Topalian SL, et al. N. Engl. J. Med. (2012) pmid: 22658127
467. Sezer A, et al. Lancet (2021) pmid: 33581821
468. Shim et al., 2020; ESMO Abstract 1269P
469. Vassal et al., 2015; ASCO Abstract 2595

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

470. Li et al., 2015; ASCO Abstract 8090
471. Benderra MA, et al. J Thorac Oncol (2016) pmid: 26845121
472. Drilon A, et al. Nat. Med. (2020) pmid: 31932802
473. Landi L, et al. Clin. Cancer Res. (2019) pmid: 31416808
474. Moro-Sibilot D, et al. Ann. Oncol. (2019) pmid: 31584608
475. Awad MM, et al. Lung Cancer (2019) pmid: 31200835
476. Shaw et al., 2016; ASCO Abstract 9066
477. Lu et al., 2016; ASCO Abstract 9058
478. Yoshida T, et al. J. Clin. Oncol. (2016) pmid: 27354483
479. Solomon BJ, et al. N. Engl. J. Med. (2014) pmid: 25470694
480. Shaw AT, et al. N. Engl. J. Med. (2013) pmid: 23724913
481. Owonikoko et al., 2019; ASCO Abstract 9022
482. Shaw AT, et al. N. Engl. J. Med. (2014) pmid: 25264305
483. Mazières J, et al. J. Clin. Oncol. (2015) pmid: 25667280
484. Scheffler M, et al. Oncotarget (2015) pmid: 25868855
485. Vaishnavi A, et al. Nat. Med. (2013) pmid: 24162815
486. Drilon et al., 2016; ASCO Abstract 108
487. Camidge et al., 2014; ASCO Abstract 8001
488. Schrock AB, et al. J Thorac Oncol (2016) pmid: 27343443
489. Jorge SE, et al. Lung Cancer (2015) pmid: 26791794
490. Mahjoubi L, et al. Invest New Drugs (2016) pmid: 26892698
491. Zhang Y, et al. J Thorac Oncol (2016) pmid: 26724472
492. Caparica R, et al. J Thorac Oncol (2017) pmid: 27664533
493. York ER, et al. J Thorac Oncol (2017) pmid: 28274743
494. Dagogo-Jack I, et al. Clin Cancer Res (2020) pmid: 32086345
495. Oaknin A, et al. JAMA Oncol (2020) pmid: 33001143
496. Subramanian et al., 2020; ESMO Abstract 1399P
497. Andre et al., 2021; ASCO GI Abstract 9
498. Gabrail et al., 2019; ASCO Abstract 2560
499. Berton et al., 2021; ASCO Abstract 2564
500. Andre et al., 2021; ESMO GI Abstract SO-9
501. Disis et al., 2016; ASCO Abstract 5533
502. Dirix et al., 2016; SABCS Abstract S1-04
503. Verschraegen et al., 2016; ASCO Abstract 9036
504. Gulley et al., 2015; ECC Abstract 3090
505. Powles et al., 2017; ASCO Genitourinary Abstract 286
506. Paz-Ares L, et al. Ann. Oncol. (2020) pmid: 32209338
507. Faivre-Finn C, et al. J Thorac Oncol (2021) pmid: 33476803
508. Planchard D, et al. Ann. Oncol. (2020) pmid: 32201234
509. Rizvi NA, et al. JAMA Oncol (2020) pmid: 32271377
510. Johnson et al., 2021; WCLC Abstract PL02.01
511. Antonia SJ, et al. J Thorac Oncol (2019) pmid: 31228626
512. Garassino MC, et al. Lancet Oncol. (2018) pmid: 29545095
513. Garassino et al., 2018; WCLC Abstract P1.01-21
514. Lind et al., 2020; BTOG Abstract 113
515. Paz-Ares et al., 2019; ESMO Immuno-Oncology Congress Abstract LBA3
516. Rizvi NA, et al. J. Clin. Oncol. (2016) pmid: 27354481
517. Forde et al., 2021; AACR Abstract CT003
518. Diab A, et al. Cancer Discov (2020) pmid: 32439653
519. Hellman et al., 2017; ASCO Abstract 3001
520. Wolchok et al., 2017; ASCO Abstract 9505
521. Borghaei et al., 2020; AACR Abstract CT221
522. Paz-Ares et al., 2021; ASCO Abstract 9016
523. Reck et al., 2021; ASCO Abstract 9000
524. Godfrey J, et al. Blood (2019) pmid: 30910787
525. Mok TSK, et al. Lancet (2019) pmid: 30955977
526. Reck M, et al. J. Clin. Oncol. (2019) pmid: 30620668
527. Brahmer et al., 2020; ESMO LBA51
528. Garon EB, et al. J. Clin. Oncol. (2019) pmid: 31154919
529. Aguilar EJ, et al. Ann. Oncol. (2019) pmid: 31435660
530. Gadgeel S, et al. J. Clin. Oncol. (2020) pmid: 32150489
531. Paz-Ares L, et al. N. Engl. J. Med. (2018) pmid: 30280635
532. Paz-Ares L, et al. J Thorac Oncol (2020) pmid: 32599071
533. Garassino et al., 2020; ASCO Abstract 9521
534. Doherty et al., 2018; WCLC Abstract P1.01-16
535. Powell et al., 2019; ESMO Abstract 1483PD
536. Mansfield et al., 2019; ESMO Abstract 1482O
537. Goldberg SB, et al. Lancet Oncol. (2016) pmid: 27267608
538. Spicer et al., 2020; SITC Abstract 362
539. Gubens MA, et al. Lung Cancer (2019) pmid: 30885353
540. Niu et al., 2020; ESMO Abstract 1410P
541. Gray JE, et al. Clin. Cancer Res. (2019) pmid: 31409616
542. Brose et al., 2019; DOI: 10.1200/JCO.2019.37.8_suppl.16
543. Ramalingam SS, et al. Cancer (2021) pmid: 34478166
544. Viteri et al., 2020; ESMO Abstract 1286P
545. Barlesi F, et al. Lancet Oncol (2018) pmid: 30262187
546. Park K, et al. J Thorac Oncol (2021) pmid: 33845211
547. Park K, et al. Lung Cancer (2021) pmid: 33636453
548. Verschraegen CF, et al. J Immunother Cancer (2020) pmid: 32907924
549. Galffy et al., 2020; SITC Abstract 281
550. Shafique M, et al. Clin Cancer Res (2021) pmid: 33820783
551. Tfayli A, et al. Cancer Med (2020) pmid: 32991781
552. Klempner SJ, et al. J Thorac Oncol (2017) pmid: 27693535
553. Yakes FM, et al. Mol. Cancer Ther. (2011) pmid: 21926191
554. Weber H, et al. J Biomol Screen (2014) pmid: 25260782
555. Navis AC, et al. PLoS ONE (2013) pmid: 23484006
556. Yeh I, et al. Nat Commun (2015) pmid: 26013381
557. Lee YH, et al. Cancers (Basel) (2014) pmid: 25534569
558. Torres KE, et al. Clin. Cancer Res. (2011) pmid: 21540237
559. Sameni M, et al. Clin. Cancer Res. (2016) pmid: 26432786
560. Hellerstedt BA, et al. Clin Lung Cancer (2019) pmid: 30528315
561. Neal JW, et al. Lancet Oncol. (2016) pmid: 27825638
562. Nokihara H, et al. Clin Lung Cancer (2019) pmid: 30718102
563. de Bono et al., 2020; ASCO GU Abstract 119
564. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
565. Mirza MR, et al. N. Engl. J. Med. (2016) pmid: 27717299
566. Mirza et al., 2016; ASCO Abstract 5555
567. Postel-Vinay et al., 2021; DOI: 10.1016/S1556-0864(21
568. Garcia-Campelo R, et al. Lung Cancer (2020) pmid: 33070053
569. Riess et al., 2021; ASCO Abstract 9024
570. Swisher EM, et al. Lancet Oncol. (2017) pmid: 27908594
571. Shapira-Frommer et al., 2015; ASCO Abstract 5513
572. Drew Y, et al. Br. J. Cancer (2016) pmid: 27002934
573. Kristeleit et al., 2014; ASCO Abstract 2573
574. Domcheck et al., 2016; ASCO Abstract 4110
575. Plummer R, et al. Cancer Chemother. Pharmacol. (2013) pmid: 23423489
576. Plummer R, et al. Clin. Cancer Res. (2008) pmid: 19047122
577. Wilson RH, et al. Br. J. Cancer (2017) pmid: 28222073

Electronically signed by Erik Williams, M.D. | 14 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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