PATIENT
DISEASE Lung non-small cell lung carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

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

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
MET exon 14 splice site (3024_3028+17del22)	Tabrecta™ (Capmatinib)

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

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

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

Microsatellite Status MS-Stable §
Tumor Mutational Burden 8 Muts/Mb §
CD274 (PD-L1) amplification §
CDKN2A loss §
INPP4B E916*
JAK2 amplification §
PDCD1LG2 (PD-L2) amplification §
PTCH1 E1439*
PTCH1 G43E

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

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

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

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

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

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

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

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	Tabrecta™ (Capmatinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E and V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre™ (Pemigatinib)

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

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

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Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 8 Muts/Mb

Genomic Findings

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

CD274 (PD-L1) amplification
MET exon 14 splice site (3024_3028+17del22)
PDCD1LG2 (PD-L2) amplification
PTCH1 G43E - subclonal, E1439*†
CDKN2A/B CDKN2A loss
INPP4B E916*
JAK2 amplification

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

† See About the Test in appendix for details.

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

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 8 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
CD274 (PD-L1) - amplification	Atezolizumab	1	Avelumab
	Durvalumab	1	Cemiplimab
	Nivolumab	1	
10 Trials *see p. 14*	Pembrolizumab	1	
PDCD1LG2 (PD-L2) - amplification	Atezolizumab	1	Avelumab
	Durvalumab	1	Cemiplimab
	Nivolumab	1	
10 Trials *see p. 18*	Pembrolizumab	1	
MET - exon 14 splice site (3024_3028+17del22)	Capmatinib	2A	Cabozantinib
10 Trials *see p. 16*	Crizotinib	2A	
PTCH1 - G43E - subclonal, E1439*	none		Sonidegib
6 Trials *see p. 20*			Vismodegib

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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

FREQUENCY & PROGNOSIS

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]. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Feb 2020). One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[6].

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
8 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[22-24] and anti-PD-1 therapies[22-25]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb; similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb[22-23,26-36]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[37], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[38], 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[39]. 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[40]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[41-42], several other large studies did find a strong association with increased TMB[43-46]. 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[47]. 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)[41]. 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[48]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[48-49].

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[50-51] and cigarette smoke in lung cancer[26,52], treatment with temozolomide-based chemotherapy in glioma[53-54], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[55-59], and microsatellite instability (MSI)[55,58-59]. 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[22-23,26-36].

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GENE
CD274 (PD-L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

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 overall survival (OS) with the PD-L1 antibody atezolizumab[60-62]. Compared with PD-L1-negative patients, clinical studies with the PD-L1 antibody durvalumab have suggested higher response rates for patients with urothelial carcinoma and PD-L1-positive tumor or immune cells[63-64], non-small cell lung cancer and PD-L1-positive tumor cells[65-66] , or head and neck squamous cell carcinoma and PD-L1-positive tumor cells[67-68] . The PD-1 antibodies pembrolizumab and nivolumab have elicited significant clinical responses in solid tumors[69], including in patients with Hodgkin lymphoma, a tumor type that harbors frequent PD-L1 copy number gains[70-71]. Clinical studies have reported that PD-L1 amplification[69] or expression[72-73] in solid tumors is associated with response to anti-PD-1 antibodies. 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[74-75]. 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[76-77]. Higher PD-L1 expression in non-small cell lung cancer (NSCLC) has been correlated with poor patient prognosis in multiple studies[78-80].

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[81-82]. These signals can help PD-L1-expressing tumor cells evade immune detection by natural killer cells or T-cells[83-85]. PD-L1 amplification has been reported to be associated with increased expression[71,74,86-87].

GENE
MET

ALTERATION
exon 14 splice site (3024_3028+17del22)

TRANSCRIPT NUMBER
NM_000245

CODING SEQUENCE EFFECT
3024_3028+17del22

POTENTIAL TREATMENT STRATEGIES

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. MET inhibitors crizotinib, capmatinib, PF-04217903, tepotinib, glesatinib, and foretinib have provided benefit to patients with MET-mutated papillary renal cell carcinoma[88-90], histiocytic sarcoma[91], and NSCLC of varied histologies[92-96]. 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 to patients who were not treated with a MET inhibitor[97]. Tepotinib showed durable clinical activity in patients with NSCLC with MET exon 14 skipping mutations, achieving a mDOR of 14.3 months, an ORR of 47.5% (47/99), and a DCR of 69.7%[98]. In another study, 11 patients with hereditary papillary renal cell carcinoma and germline MET mutations (4 of which were H1094R) experienced 5 PR and 5 SD after treatment with foretinib[88]. 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 NSCLCs reported 16/31 (52%) of patients achieved a PR[99].

FREQUENCY & PROGNOSIS

In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in 3% of samples[91]. In the TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[76-77]. 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[100-108]. Studies on the effect of MET amplification on prognosis in NSCLC have yielded conflicting results[100,104,106,109-113], although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[114]. 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[115]. 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[116-117]. 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)[97].

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[118-119]. Certain MET alterations have been associated with the removal of exon 14[93,120-124] and/or loss of a binding site for the ubiquitin ligase CBL, an enzyme that targets MET for degradation[120,125-127]. 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[120,124,126-130]; 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[91,93,131-135].

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GENE
PDCD1LG2 (PD-L2)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

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[136-144], and Hodgkin lymphoma, which harbors frequent PD-L2 copy number gains[70-71]. 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[61-62,145]. 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[74-75]. 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[146].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PDCD1LG2 amplification was observed in 3% of lung squamous cell carcinoma (SCC) cases[77] and <1% of cases in the Lung Adenocarcinoma TCGA dataset[76]. 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[147]. 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[148].

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[81-82]. 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[149-150].

GENE
PTCH1

ALTERATION
G43E - subclonal, E1439*

TRANSCRIPT NUMBER
- NM_001083603
- NM_000264

CODING SEQUENCE EFFECT
- 128G>A
- 4315G>T

POTENTIAL TREATMENT STRATEGIES

Loss of PTCH1 function results in ligand-independent and constitutive activation of SMO and downstream Hh signaling, and may predict sensitivity to SMO inhibitors[151-154] such as vismodegib and sonidegib. Significant clinical responses to vismodegib or sonidegib have been observed in patients with basal cell carcinoma or medulloblastoma with activated Hedgehog signaling[155-158], including in patients harboring PTCH1 mutations[156-158]; in one study, PTCH1 copy number loss was significantly associated with improved progression-free survival in patients with SHH-subtype medulloblastoma[158]. The transcriptional activity of the GLI transcription factors have been shown to be dependent on the bromo and extra C-terminal (BET) bromodomain protein BRD4; preclinical studies have shown that the BET inhibitor JQ1 results in downregulation of GLI transcriptional activity[159]. Therefore, BET inhibitors may be a relevant therapeutic approach for cancers with PTCH1 loss or inactivation. BET inhibitors are in clinical trials for multiple cancer types. 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

PTCH1 mutations have been reported in 5% of lung adenocarcinoma and 1% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA datasets[76-77]. PTCH1 has been shown to be overexpressed in non-small cell lung carcinoma (NSCLC) tumors, with higher expression in SCC than in adenocarcinoma[160]. Loss of PTCH1 has also been observed in lung SCC, and correlated with poor patient prognosis[161].

FINDING SUMMARY

The PTCH1 tumor suppressor gene encodes a 12-transmembrane protein that functions as an inhibitor of Smoothened (SMO) and downstream Hedgehog (Hh) signaling[162]. PTCH1 is a receptor for Hh ligands[163] and Hh ligand binding to PTCH1 results in derepression of SMO and downstream activation GLI-family transcription factors[164]. Inactivating germline mutations in PTCH1 are associated with Basal Cell Nevus Syndrome (Gorlin syndrome)[165-166]. Patients with Gorlin syndrome develop basal cell carcinomas and are also predisposed to medulloblastoma. Somatic mutations that inactivate PTCH1 are frequently found in the sporadic forms of these cancers. Although PTCH1 truncation mutations that affect the C-terminal cytoplasmic tail, such as E1439* observed here, have been reported to repress SMO-GLI1 signaling similarly to wild-type PTCH1[167-168], the PTCH1 C-terminus may be important for signaling that is independent of the canonical Hh pathway[168-170], and it is not known if such truncation mutations predict response to SMO inhibitors. Although alterations such as G43E 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.

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GENE
CDKN2A/B

ALTERATION
CDKN2A loss

POTENTIAL TREATMENT STRATEGIES

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[171-174]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[175-176], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[177-183]; 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[184-185], 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[76]. 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[77]. 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[77,186-191]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[188,192-194].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[195-196]. 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[187,197]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[198-199]. This alteration is predicted to result in p16INK4a[200-221] loss of function. This alteration is predicted to result in p14ARF[204,221-224] loss of function. This alteration does not affect the function of p15INK4b.

GENE
INPP4B

ALTERATION
E916*

TRANSCRIPT NUMBER
NM_003866

CODING SEQUENCE EFFECT
2746G>T

POTENTIAL TREATMENT STRATEGIES

There are no approved drugs targeting INPP4B loss or mutation. Multiple preclinical studies have shown that loss or inactivation of INPP4B leads to activation of the PI3K-AKT pathway[225-227]. However, sensitivity of tumors harboring INPP4B alterations to inhibitors of this pathway has not been tested clinically or preclinically.

FREQUENCY & PROGNOSIS

INPP4B mutations have been reported in 5% of cancers across all subtypes, with highest prevalence in carcinomas of the liver (19%), pancreas (13%), prostate (12%), breast (8%), and esophagus (8%) (COSMIC, 2020). Loss of heterozygosity at the INPP4B locus in basal-like breast cancer is correlated with reduced overall survival[225-226]. Reduced expression of INPP4B is also observed in lung cancer, prostate cancer, and acute lymphoblastic leukemia (ALL) in children with Down syndrome[228-230], and has been associated with reduced time to recurrence in prostate cancer[229]. Collectively, these data suggest a tumor suppressor role for INPP4B.

FINDING SUMMARY

INPP4B encodes an enzyme that negatively regulates the PI3K-AKT pathway and behaves as a tumor suppressor[225-227,231-232].

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GENE
JAK2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

On the basis of a case report in chronic myelomonocytic leukemia[233] and extensive clinical data in myelofibrosis, a disease type that frequently harbors the JAK2 V617F mutation[146,234-236], JAK2 activating mutations may predict sensitivity to JAK2 inhibitors such as ruxolitinib. The JAK2 inhibitor fedratinib has been used to treat patients with myelofibrosis, with responses observed for both JAK2 V617F-positive and -negative patients, including patients resistant (spleen response rate [RR] = 52.7% [29/55]) or intolerant (spleen RR = 63.0% [17/27]) to ruxolitinib[237-238]. JAK2 activating alterations may predict sensitivity to HDAC inhibitors[239-241]; a Phase 1/2 study of givinostat for patients with JAK2 V617F-mutated polycythemia vera reported ORRs of 72.7% (8/11, 1 CR) to 80.7% (25/31, 3 CRs) across trial arms[242]. Other alterations that activate JAK2, such as fusions[243-249] or amplifications[250-251], may also confer sensitivity to JAK2 inhibitors, on the basis of clinical data in myeloid neoplasms as well as preclinical data. Preclinical studies have suggested that activating alterations in JAK2 may confer sensitivity to HSP90 inhibitors[252-253].

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[76-77]. 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[254-255]. High expression of the JAK2-STAT3 pathway has been associated with decreased survival in patients with NSCLC[255].

FINDING SUMMARY

JAK2 encodes Janus kinase 2, a tyrosine kinase that regulates signals triggered by cytokines and growth factors[256]. 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[74,247].

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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, triple-negative breast cancer, and hepatocellular carcinoma. 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[61,145,257] . 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[61,145,257] .

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[258]. 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[259-261] . 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[260]. 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[259]. 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[261]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic NSCLC reported improved median OS (20.2 vs. 13.1 months; HR=0.60), median PFS (8.1 vs. 5.0 months), and ORR (38.3% vs. 28.6%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[262]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in median OS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[263], confirming previous Phase 2 trial data[61,264] . Clinical benefit was observed for patients regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was achieved with tumor PD-L1 expression >50% (HR=0.41) compared with <1% (HR=0.75)[263]. Retrospective analysis of the OAK trial revealed numerically improved ORR in patients receiving concomitant atezolizumab and metformin compared with atezolizumab alone (25% vs. 13%), but no difference in PFS or OS with the addition of metformin[265].

Capmatinib

Assay findings association

MET
exon 14 splice site (3024_3028+17del22)

AREAS OF THERAPEUTIC USE

Capmatinib is a Type Ib MET inhibitor that is FDA approved to treat patients with metastatic non-small cell lung cancer harboring MET exon 14 skipping-associated alterations.

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[266-268] , MET mutations associated with exon 14 skipping may predict sensitivity to capmatinib.

SUPPORTING DATA

Capmatinib monotherapy has demonstrated clinical efficacy for patients with advanced NSCLC harboring MET exon 14 skipping alterations and lacking EGFR mutations or ALK-rearrangements[266-267] . 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 (9.7 vs 5.4 months) and median DOR (11.4 vs 9.72 months) for treatment-naive patients when compared with those who had prior therapies; no correlation was observed between patient responses and the presence of co-occurring MET amplification[266]. This study additionally recorded a 53.8% (7/13) intracranial response rate and 92.3% (12/13) intracranial DCR[266]. In a Phase 1 study for MET-dysregulated advanced NSCLC, patients with exon 14 splicing mutations achieved 3 confirmed PRs and 1 unconfirmed PR (n=4)[267]. 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)[269], gastric cancer (n=9), or other advanced solid tumors (n=24)[270-271] .

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Crizotinib

Assay findings association

MET
exon 14 splice site
(3024_3028+17del22)

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are positive for ALK rearrangements or ROS1 rearrangements.

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)[272-276] , gastric cancer[277], gastroesophageal cancer[278], glioblastoma[279], and carcinoma of unknown primary[280], as well as in patients with MET-mutated cancers, including NSCLC[91,93-96,281] , renal cell carcinoma (RCC)[90], and histiocytic sarcoma[91]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[91,93-97] .

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[282]. 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[283-284] . A retrospective study reported median PFS of 7.4 months in patients with MET exon 14-altered NSCLC treated with crizotinib[285]. 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[273]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[286-290] , ROS1 rearrangements[284,291-294] , an NTRK1 fusion[295], or MET activation[93-96,123,272-276,281,296-301] .

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

GENE ASSOCIATION

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[61,63-68,145,257,302-305] . 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[61,145,257] .

SUPPORTING DATA

In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable NSCLC who did not have progression on chemoradiotherapy (CT), durvalumab monotherapy was superior to placebo, including for median PFS (mPFS) (17.2 vs. 5.6 months, HR=0.51), median OS (mOS) (HR=0.68, p=0.0025) and ORR (30.0% vs. 17.8%, p<0.001)[306-307] . Superior OS elicited by durvalumab monotherapy in EGFR/ALK-negative metastatic NSCLC with tumor cell PD-L1 expression ≥25% was also reported in the Phase 3 MYSTIC trial for treatment-naive patients in comparison to CT (HR=0.63)[308] and in the Phase 3 ARCTIC study for patients with 2 or fewer prior therapies in comparison with standard of care (HR=0.63; 11.7 months vs. 6.8 months)[309]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[310-311] and OS[310] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90% tumor cells with PD-L1 staining) had an ORR of 30.9% (21/68), compared with ORRs of 16.4% (24/146) for patients with ≥25% of tumor cells and 7.5% (7/93) for patients with <25% of tumor cells with PD-L1 staining, respectively[311]. Retreatment with durvalumab in patients with PD-L1-positive (≥25%), EGFR/ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or an SD for 25.0% (10/40) of patients[312]. Durvalumab in combination with nab-paclitaxel for patients with previously treated advanced NSCLC elicited mPFS of 4.5 months and an ORR of 27%[313], whereas a combination with tremelimumab and durvalumab elicited an ORR of 18.8% (40/213) for patients with non-squamous NSCLC[314] and improved OS versus CT for patients with NSCLC with tumor cell PD-L1 expression ≥25% (HR=0.64)[308].

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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 in various treatment settings for patients with renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, classical Hodgkin lymphoma (cHL), and metastatic small cell lung cancer (SCLC). Furthermore, nivolumab is approved as both a single agent and in combination with ipilimumab to treat patients with melanoma, non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), and mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Please see the drug label for full prescribing information.

GENE ASSOCIATION

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[73,315] .

SUPPORTING DATA

For patients with platinum-refractory non-squamous non-small cell lung cancer (NSCLC), nivolumab improved median OS (12.2 vs. 9.4 months) and ORR (19% vs. 12%) compared with docetaxel in the Phase 3 CheckMate 057 study; PD-L1 expression was associated with OS benefit from nivolumab in this study (HR=0.40–0.59)[142]. In advanced squamous NSCLC, second-line nivolumab resulted in longer median OS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel in the Phase 3 CheckMate 017 study; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[141,143] . Pooled analysis of CheckMate 057 and CheckMate 017 showed improved long-term OS and PFS benefit for nivolumab over docetaxel, with 5-year OS rates of 13.4% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[316]. Combination of nivolumab with the CTLA4-targeting antibody ipilimumab improved median OS for patients with advanced NSCLC relative to chemotherapy regardless of PD-L1 positivity or TMB status (17.1 vs. 13.9 months, HR=0.73) in the Phase 3 CheckMate 227 study[38], despite earlier analysis of this trial which suggested improved PFS only for patients with TMB ≥10 muts/Mb[31]. In another arm of the CheckMate 227 study, combination of nivolumab with platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[317], despite Phase 1 results in the same setting suggesting improved ORR and OS[318].

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

GENE ASSOCIATION

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[319] and in a lasting PR in a patient with CD274-amplified cancer of unknown primary[69]. PD-L1 expression is associated with significantly prolonged median OS for patients with EGFR/ALK wildtype advanced NSCLC treated with pembrolizumab compared with chemotherapy[320-322] . 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[72]. 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[73].

SUPPORTING DATA

The superiority of pembrolizumab over platinum chemotherapy for the first-line treatment of patients with PD-L1-positive NSCLC lacking EGFR or ALK alterations was demonstrated in the Phase 3 KEYNOTE-042 and -024 studies, which reported improved median OS (mOS) for PD-L1 tumor proportion scores (TPS) ≥1% (16.7 vs. 12.1 months, HR=0.81)[320] and ≥50% (20.0–30.0 vs. 12.2–14.2 months, HR=0.63-0.69)[320-321] . In the Phase 1b KEYNOTE-100 study of pembrolizumab, mOS was numerically higher for patients with NSCLC and PD-L1 TPS ≥50% relative to those with lower levels of expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[323]. A retrospective study showed that among patients with NSCLC and high PD-L1 expression treated with first-line pembrolizumab, mOS was improved for patients with TPS 90% to 100% relative to those with TPS 50% to 89% (not reached vs. 15.9 months, HR=0.39)[324]. 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)[325] or squamous (KEYNOTE-407)[326] NSCLC, regardless of PD-L1 status. For the first-line treatment of patients with NSCLC and high PD-L1 expression (TPS ≥50%), a meta-analysis of KEYNOTE-024 and -189 reported the combination of pembrolizumab and chemotherapy to be non-superior to pembrolizumab alone in terms of survival benefit; however, the combination did increase ORR (+21.5%, p=0.011)[327]. 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[322]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single-agent and in combination with chemotherapy, for the treatment of patients with NSCLC and brain metastases[328-330] . Clinical activity has also been achieved with pembrolizumab in combination with ipilimumab[331], the HDAC inhibitor vorinostat[332], and the multikinase inhibitor lenvatinib[333].

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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[61,145,257,302-305] . 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[61,145,257] .

SUPPORTING DATA

In a Phase 1b study evaluating single-agent avelumab for the treatment of patients with non-small cell lung cancer (NSCLC), the ORR was 12% (22/184) in previously treated patients and 18.7% (14/75) in the first-line setting, and the median PFS was 12 weeks for both cohorts[304,334]. In patients with NSCLC and PD-L1-positive tumor cells, first-line treatment with avelumab resulted in numerically increased ORR (20%; 7/35 vs. 0%; 0/10) and a trend toward prolonged PFS (11.6 vs. 6.0 weeks) relative to patients with fewer than 1% of tumor cells expressing PD-L1[304]; however, response rates, PFS, and OS were similar regardless of immune or tumor cell PD-L1 expression in patients who had previously received platinum-based treatment[334].

Cabozantinib

Assay findings association

MET
exon 14 splice site (3024_3028+17del22)

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved to treat patients with advanced renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) after prior treatment with sorafenib, or progressive, metastatic medullary thyroid cancer (MTC).

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[93,335] , as well as by extensive preclinical data[336-342] .

SUPPORTING DATA

Cabozantinib elicited a CR in a patient with lung adenocarcinoma harboring a MET amplification and a mutation affecting MET exon 14 splicing[93]. 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[343]. 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[344]. 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[345].

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

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[70-73,315,322,346-347] and may predict sensitivity to cemiplimab.

SUPPORTING DATA

A Phase 1 trial for patients with advanced NSCLC reported a 40% ORR (8/20; 1 CR and 7 PRs) and 60% DCR following treatment with cemiplimab monotherapy and an 18.2% ORR (6/33; 6 PRs) and 73% DCR for patients who received cemiplimab and radiotherapy[348].

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Sonidegib

Assay findings association

PTCH1
G43E - subclonal, E1439*

AREAS OF THERAPEUTIC USE

Sonidegib is a small-molecule inhibitor of the protein Smoothened (SMO), a member of the Hedgehog signaling pathway. Sonidegib is FDA approved to treat locally advanced, recurrent basal cell carcinoma (BCC) that is not amenable to surgery or radiation therapy.

GENE ASSOCIATION

Alterations that inactivate PTCH1 may predict sensitivity to SMO inhibitors such as sonidegib, which has shown significant clinical activity in patients with Hh pathway-activated BCC or medulloblastoma[155,349-350] . 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

Clinical data on the efficacy of sonidegib for the treatment of NSCLC are limited (PubMed, Apr 2020). Studies of sonidegib have largely focused on basal cell carcinoma (BCC) and medulloblastoma, 2 diseases associated with activated Hedgehog pathway (Hh) signaling. The Phase 2 BOLT trial demonstrated ORRs of 56.1% (37/66) and 46.1% (59/128) for patients with locally advanced BCC (laBCC) receiving 200mg or 800mg sonidegib, respectively, and 7.7% (1/13) and 17.4% (4/23) for patients with metastatic BCC (mBCC) receiving 200mg or 800mg dose, respectively[351]. The DCR was greater than 90% for patients with either laBCC or mBCC given the 200mg dose and 82% and 91% for patients with laBCC and mBCC treated with the 800mg dose[351]. In 3 Phase 1 studies, 4/6 adults and 2/3 pediatric patients with medulloblastoma and a high Hh gene signature experienced a response to sonidegib, whereas 0/7 adults and 0/34 pediatric patients with a non-Hh gene signature responded[155]. A Phase 1 clinical trial of sonidegib for solid tumors reported SD for 23.3% of patients (24/103), lasting greater than 6 months for 3 patients with lung adenocarcinoma, spindle cell sarcoma, and BCC; ORRs of 37.5% (6/16; 1 CR, 3 PRs) in BCC and 33.3% (3/9; 2 PRs) in medulloblastoma were reported in this study[349]. For patients with advanced solid tumors that are refractory to standard therapy and progressed on second-line therapy, a Phase 1 trial of sonidegib combined with paclitaxel established a safe and tolerable dose and achieved PR in 2 ovarian and 1 breast cancer patients[352].

Vismodegib

Assay findings association

PTCH1
G43E - subclonal, E1439*

AREAS OF THERAPEUTIC USE

Vismodegib is a small molecule inhibitor of the protein Smoothened (SMO), a member of the Hedgehog signaling pathway. Vismodegib has been approved by the FDA for the treatment of locally advanced and metastatic basal cell carcinoma (BCC).

GENE ASSOCIATION

Based on strong clinical evidence in BCC[156] and medulloblastoma[155,157-158] , alterations that inactivate PTCH1 may predict sensitivity to vismodegib. In one study of patients with medulloblastoma treated with vismodegib, PTCH1 copy number loss was significantly associated with improved progression-free survival[158]. 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

Clinical data on the efficacy of vismodegib for the treatment of NSCLC are limited (PubMed, Apr 2020). Studies of vismodegib have largely focused on BCC and medulloblastoma, which are disease types associated with activated Hedgehog pathway signaling. In the ERIVANCE BCC Phase 2 study, 43% of patients with locally advanced BCC experienced a partial or complete response, whereas 21% of patients with metastatic BCC experienced a complete response[353]. In two Phase 2 studies of vismodegib for recurrent or refractory medulloblastoma, 8 of 26 (31%) patients with SHH-subtype medulloblastoma (SHH-MB) had a response to vismodegib, whereas none of 9 patients with non-SHH-MB had a response; vismodegib also resulted in significantly improved progression-free survival for patients with SHH-MB compared to patients with non-SHH-MB[158]. Significant responses to vismodegib in patients with medulloblastoma have also been reported in other studies[157,354-355] , including responses in patients with SHH-MB[355] or in patients harboring a PTCH1 mutation[157]. A Phase 1 clinical trial of vismodegib in patients with solid tumors reported tumor response in 29% (20/68, including 19 patients with BCC and one with medulloblastoma), stable disease in 20% (14/68), and tumor progression in 41% (28/68) of patients[354]. Another Phase 1 clinical trial of vismodegib in patients with solid tumors was unable to achieve the unbound plasma concentrations that have been associated with efficacy in BCC and medulloblastoma[356].

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

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CLINICAL TRIALS

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

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 anti-tumor immune response. Antibodies that block the interaction of PD-L1 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-L1 expression.

NCT03793179

PHASE 3

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

TARGETS
PD-1

LOCATIONS: Kentucky, Ohio, Virginia

NCT03829332

PHASE 3

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

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

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

NCT03924869

PHASE 3

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

TARGETS
PD-1

LOCATIONS: Kentucky, Indiana, Tennessee, Mississauga (Canada), Pennsylvania, New Jersey, New York, Kingston (Canada), Sault Ste Marie (Canada)

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

LOCATIONS: Kentucky, London (Canada), Maryland, Toronto (Canada), New York, Pennsylvania, New Jersey

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: Kentucky, Pennsylvania, North Carolina, Illinois, Maryland, South Carolina, New Jersey, Florida

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CLINICAL TRIALS

NCT03631706

PHASE 3

M7824 Versus Pembrolizumab as a First-line (1L) Treatment in Participants With Programmed Death-ligand 1 (PD-L1) Expressing Advanced Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-1, PD-L1, TGF-beta

LOCATIONS: Kentucky, Tennessee, Alabama, Ohio, Pennsylvania, Illinois, Michigan, Virginia

NCT03906071

PHASE 3

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

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

LOCATIONS: Kentucky, Ohio, Tennessee, Indiana, Alabama, Georgia

NCT02834013

PHASE 2

Nivolumab and Ipilimumab in Treating Patients With Rare Tumors

TARGETS
CTLA-4, PD-1

LOCATIONS: Kentucky, Ohio, West Virginia

NCT03822351

PHASE 2

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

TARGETS
PD-L1, CD73, NKG2A

LOCATIONS: Kentucky, West Virginia, Illinois, Virginia, Maryland, Tennessee, Pennsylvania

NCT03170960

PHASE 1/2

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

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

LOCATIONS: Kentucky, Ohio, Virginia, Pennsylvania, Georgia, Michigan, Illinois, District of Columbia

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GENE
MET

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

ALTERATION
exon 14 splice site (3024_3028+17del22)

NCT03906071

PHASE 3

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

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

LOCATIONS: Kentucky, Ohio, Tennessee, Indiana, Alabama, Georgia

NCT03539536

PHASE 2

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

TARGETS
MET

LOCATIONS: Kentucky, Tennessee, Michigan, Illinois, Missouri, Virginia, Wisconsin

NCT03170960

PHASE 1/2

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

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

LOCATIONS: Kentucky, Ohio, Virginia, Pennsylvania, Georgia, Michigan, Illinois, District of Columbia

NCT02864992

PHASE 2

Tepotinib Phase II Study in Lung Adenocarcinoma Harbouring MET Exon 14 (METex14) Skipping Alterations

TARGETS
MET

LOCATIONS: Ohio, Indiana, Tennessee, Georgia, Illinois, Missouri, Virginia, New Jersey

NCT02954991

PHASE 2

Phase 2 Study of Glesatinib, Sitravatinib or Mocetinostat in Combination With Nivolumab in Non-Small Cell Lung Cancer

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

LOCATIONS: Ohio, Kentucky, Tennessee, Michigan, Virginia, Wisconsin, Minnesota, Texas

NCT03175224

PHASE 1/2

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

TARGETS
MET

LOCATIONS: Ohio, South Carolina, West Virginia, North Carolina, Wisconsin, Delaware, Florida, Minnesota, Arizona

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NCT02693535

PHASE 2

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

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

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

NCT02099058

PHASE 1

A Phase 1/1b Study With ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Cancer Tumors

TARGETS
MET, EGFR, PD-1

LOCATIONS: Tennessee, Michigan, North Carolina, Illinois, Virginia, Massachusetts, Texas, Colorado, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT02795156

PHASE 2

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

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

LOCATIONS: Tennessee, Wisconsin, Missouri, Florida, Colorado

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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.

NCT03793179

PHASE 3

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

TARGETS
PD-1

LOCATIONS: Kentucky, Ohio, Virginia

NCT03829332

PHASE 3

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

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

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

NCT03924869

PHASE 3

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

TARGETS
PD-1

LOCATIONS: Kentucky, Indiana, Tennessee, Mississauga (Canada), Pennsylvania, New Jersey, New York, Kingston (Canada), Sault Ste Marie (Canada)

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

LOCATIONS: Kentucky, London (Canada), Maryland, Toronto (Canada), New York, Pennsylvania, New Jersey

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: Kentucky, Pennsylvania, North Carolina, Illinois, Maryland, South Carolina, New Jersey, Florida

NCT03631706

PHASE 3

M7824 Versus Pembrolizumab as a First-line (1L) Treatment in Participants With Programmed Death-ligand 1 (PD-L1) Expressing Advanced Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-1, PD-L1, TGF-beta

LOCATIONS: Kentucky, Tennessee, Alabama, Ohio, Pennsylvania, Illinois, Michigan, Virginia

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CLINICAL TRIALS

NCT03906071

PHASE 3

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

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

LOCATIONS: Kentucky, Ohio, Tennessee, Indiana, Alabama, Georgia

NCT03822351

PHASE 2

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

TARGETS
PD-L1, CD73, NKG2A

LOCATIONS: Kentucky, West Virginia, Illinois, Virginia, Maryland, Tennessee, Pennsylvania

NCT03170960

PHASE 1/2

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

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

LOCATIONS: Kentucky, Ohio, Virginia, Pennsylvania, Georgia, Michigan, Illinois, District of Columbia

NCT04165070

PHASE 2

Substudy 1: Efficacy and Safety Study of Pembrolizumab (MK-3475) Plus Chemotherapy When Used With Investigational Agents in Treatment-naïve Participants With Advanced Non-small Cell Lung Cancer (NSCLC) (MK-3475-01A/KEYNOTE-01A)

TARGETS
PD-1

LOCATIONS: Kentucky, Ohio, Maryland, Nebraska, California

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GENE
PTCH1

ALTERATION
G43E - subclonal, E1439*

RATIONALE
Loss or inactivation of the tumor suppressor PTCH1 upregulates the activity of the Hedgehog pathway member Smoothened (SMO), which may contribute to excessive cell proliferation. Inhibitors of SMO or BET-domain containing transcription factors may be relevant in a tumor with a loss or inactivation of PTCH1. 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.

NCT03205176

PHASE 1

AZD5153 in Patients With Relapsed or Refractory Solid Tumors, Including Lymphomas

TARGETS
BRD4, PARP

LOCATIONS: Tennessee, Florida, Oklahoma

NCT02419417

PHASE 1/2

Study of BMS-986158 in Subjects With Select Advanced Solid Tumors

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: South Carolina, Pennsylvania, Ottawa (Canada), Massachusetts, Colorado, California, Oregon, Madrid (Spain), Villejuif (France), Pamplona (Spain)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

LOCATIONS: Virginia, New York, Florida, Texas, Arizona

NCT02516553

PHASE 1

BI 894999 First in Human Dose Finding Study in Advanced Malignancies

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Massachusetts, Gent (Belgium), Villejuif (France), Brussels (Belgium), Bruxelles (Belgium), Leuven (Belgium), Tübingen (Germany)

NCT03220347

PHASE 1

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Madrid (Spain), Bordeaux (France), Villejuif (France), Barcelona (Spain), Rozzano (MI) (Italy), Meldola (Italy), Napoli, Campania (Italy)

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

BRAF
amplification

BRCA2
H2074N

EPHB1
P787T

ERCC4
S283Y

EZH2
amplification

KEL
amplification

MET
S572N and amplification

MST1R
R1388L

NTRK2
D139N

PIK3C2G
T488A

PTCH1
E48_N49insE

SMO
amplification

TYRO3
G642F and G842D

XRCC2
amplification

INTENDED USE

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

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

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

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	Tabrecta™ (Capmatinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E and V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib), in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre™ (Pemigatinib)

The median exon coverage for this sample is 764x

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

TEST PRINCIPLE

FoundationOne®CDx (F1CDx) is performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The assay employs a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons (refer to Table 2 and Table 3 for complete list of genes included in F1CDx). In total, the assay detects alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid capture–selected libraries are sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data is then processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous gene deletions), and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and positive homologous recombination deficiency (HRD) status (tBRCA-positive and/or LOH high) are reported.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/f1cdx

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
4. Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*.
5. Clinical performance of Tagrisso® (osimertinib) in patients with an *EGFR* exon 20 T790M mutation detected with an allele fraction <5% is ongoing and has not been established.
6. Concordance with other validated methods for CNA (with the exception of *ERBB2*) and gene rearrangement (with the exception of *ALK*) detection has not been demonstrated and will be provided in the post-market setting. Confirmatory testing using a clinically validated assay should be performed for all CNAs and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use, but used for clinical decision making.
7. The MSI-H/MSS designation by FMI FoundationOne®CDx (F1CDx) test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. Refer https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf for additional details on methodology. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. Patients with microsatellite status of "Cannot Be Determined" should be retested with an orthogonal (alternative) method. The clinical validity of the qualitative MSI designation has not been established.
8. TMB by F1CDx is defined based by counting the total number of all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit. TMB is a function of the characteristics of a patient's specimen and testing parameters; therefore, TMB may differ among specimens (e.g., primary vs. metastatic, tumor content) and targeted panels. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay LoD, filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has not been established.
9. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community.
10. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.
11. Alterations in polyT homopolymer runs may not be reliably detected in BRCA1/2.
12. Certain large rearrangements in BRCA1/2 including large scale genomic deletions (affecting at least one whole exon), insertions or other deleterious genomic rearrangements

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

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

PDF Service Version 2.11.0

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL AND SUBCLONAL)

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

PROFESSIONAL SERVICES FINDINGS

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

RANKING OF ALTERATIONS AND THERAPIES

Biomarker and Genomic Findings

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

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

LOSS OF HETEROZYGOSITY SCORE

The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. The LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH.

MICROSATELLITE STATUS

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

TUMOR MUTATIONAL BURDEN

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations in sequenced genes on the FoundationOne CDx test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne CDx samples and is reported in Professional Services as the number of mutations per megabase (Muts/Mb) rounded to the nearest integer. Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

Genomic Findings with Evidence of Clinical Significance

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

Genomic Findings with Potential Clinical Significance

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

A Fluid Approach to Reporting Levels

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

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

Electronically signed by J. Keith Killian, M.D. |
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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. Rizvi NA, et al. Science (2015) PMID: 25765070
27. Colli LM, et al. Cancer Res. (2016) PMID: 27197178
28. Wang VE, et al. J Immunother Cancer (2017) PMID: 28923100
29. Carbone DP, et al. N. Engl. J. Med. (2017) PMID: 28636851
30. Rizvi H, et al. J. Clin. Oncol. (2018) PMID: 29337640
31. Hellmann MD, et al. N. Engl. J. Med. (2018) PMID: 29658845
32. Hellmann MD, et al. Cancer Cell (2018) PMID: 29657128
33. Forde PM, et al. N. Engl. J. Med. (2018) PMID: 29658848
34. Ready N, et al. J. Clin. Oncol. (2019) PMID: 30785829
35. Miao D, et al. Nat. Genet. (2018) PMID: 30150660
36. Chae YK, et al. Clin Lung Cancer (2019) PMID: 30425022
37. Paz-Ares et al., 2019; ESMO Abstract LBA80
38. Hellmann MD, et al. N. Engl. J. Med. (2019) PMID: 31562796
39. Chalmers ZR, et al. Genome Med (2017) PMID: 28420421
40. Spigel et al., 2016; ASCO Abstract 9017
41. Xiao D, et al. Oncotarget (2016) PMID: 27009843
42. Shim HS, et al. J Thorac Oncol (2015) PMID: 26200269
43. Govindan R, et al. Cell (2012) PMID: 22980976
44. Ding L, et al. Nature (2008) PMID: 18948947
45. Imielinski M, et al. Cell (2012) PMID: 22980975
46. Kim Y, et al. J. Clin. Oncol. (2014) PMID: 24323028
47. Stein et al., 2019; DOI: 10.1200/PO.18.00376
48. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) PMID: 31088500
49. Yu H, et al. J Thorac Oncol (2019) PMID: 30253973
50. Pfeifer GP, et al. Mutat. Res. (2005) PMID: 15748635
51. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) PMID: 23875803
52. Pfeifer GP, et al. Oncogene (2002) PMID: 12379884
53. Johnson BE, et al. Science (2014) PMID: 24336570
54. Choi S, et al. Neuro-oncology (2018) PMID: 29452419
55. Cancer Genome Atlas Research Network, et al. Nature (2013) PMID: 23636398
56. Briggs S, et al. J. Pathol. (2013) PMID: 23447401
57. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) PMID: 24583393
58. Nature (2012) PMID: 22810696
59. Roberts SA, et al. Nat. Rev. Cancer (2014) PMID: 25568919
60. Martin-Liberal et al., 2015; ESMO Symposium on Immuno-Oncology Abstract 24P
61. Fehrenbacher L, et al. Lancet (2016) PMID: 26970723
62. Herbst RS, et al. Nature (2014) PMID: 25428504
63. Powles et al., 2017; ASCO Genitourinary Abstract 286
64. Massard C, et al. J. Clin. Oncol. (2016) PMID: 27269937
65. Bais et al., 2017; AACR Abstract 3720/5
66. Garassino et al., 2016; IASLC Abstract PLO4a.03
67. Segal et al., 2015; ASCO Abstract 3011
68. Rebelatto et al., 2015; ASCO Abstract 8033
69. Gröschel S, et al. Cold Spring Harb Mol Case Stud (2016) PMID: 27900363
70. Ansell et al., 2015; ASH Abstract 583
71. Ansell SM, et al. N. Engl. J. Med. (2015) PMID: 25482239
72. Kefford et al., 2014; ASCO Abstract 3005
73. Taube JM, et al. Clin. Cancer Res. (2014) PMID: 24714771
74. Green MR, et al. Blood (2010) PMID: 20628145
75. Derenzini E, et al. Blood Cancer J (2011) PMID: 22829094
76. Nature (2014) PMID: 25079552
77. Nature (2012) PMID: 22960745
78. Mu CY, et al. Med. Oncol. (2011) PMID: 20373055
79. Hamanishi J, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) PMID: 17360651
80. Chen YB, et al. Tumori (2012) PMID: 23389362
81. Keir ME, et al. Annu. Rev. Immunol. (2008) PMID: 18173375
82. Butte MJ, et al. Immunity (2007) PMID: 17629517
83. Benson DM, et al. Blood (2010) PMID: 20460501
84. Iwai Y, et al. Proc. Natl. Acad. Sci. U.S.A. (2002) PMID: 12218188
85. Liu J, et al. Blood (2007) PMID: 17363736
86. Nature (2014) PMID: 25079317
87. George J, et al. Clin. Cancer Res. (2017) PMID: 27620277
88. Choueiri TK, et al. J. Clin. Oncol. (2013) PMID: 23213094
89. Diamond JR, et al. J. Clin. Oncol. (2013) PMID: 23610116
90. Stein MN, et al. Eur. Urol. (2015) PMID: 25457019
91. Frampton GM, et al. Cancer Discov (2015) PMID: 25971938
92. Engstrom LD, et al. Clin. Cancer Res. (2017) PMID: 28765324
93. Paik PK, et al. Cancer Discov (2015) PMID: 25971939
94. Jenkins RW, et al. Clin Lung Cancer (2015) PMID: 25769807
95. Waqar SN, et al. J Thorac Oncol (2015) PMID: 25898962
96. Mendenhall MA, et al. J Thorac Oncol (2015) PMID: 25898965
97. Awad et al., 2017; ASCO Abstract 8511
98. Paik et al, 2019; ASCO Abstract 9005
99. Lu et al., 2019; AACR Abstract CT031
100. Dziadziuszko R, et al. J Thorac Oncol (2012) PMID: 22237262
101. Murray S, et al. J. Exp. Clin. Cancer Res. (2012) PMID: 22992338
102. Xia N, et al. Exp. Lung Res. (2013) PMID: 23919423
103. Nakamura Y, et al. Cancer Sci. (2007) PMID: 17459054
104. Park S, et al. Histol. Histopathol. (2012) PMID: 22207554
105. Spigel DR, et al. J. Clin. Oncol. (2013) PMID: 24101053
106. Cappuzzo F, et al. J. Clin. Oncol. (2009) PMID: 19255323
107. Zucali PA, et al. Ann. Oncol. (2008) PMID: 18467317
108. An SJ, et al. PLoS ONE (2012) PMID: 22768234
109. Yang JJ, et al. Lung Cancer (2013) PMID: 23079155
110. Chen YT, et al. J Thorac Oncol (2011) PMID: 22052229
111. Kanteti R, et al. J. Environ. Pathol. Toxicol. Oncol. (2009) PMID: 19817696
112. To C, et al. Exp. Cell Res. (2002) PMID: 11795945
113. Tsuta K, et al. J Thorac Oncol (2012) PMID: 22198430
114. Tanaka A, et al. Lung Cancer (2012) PMID: 21733594
115. Tong JH, et al. Clin. Cancer Res. (2016) PMID: 26847053
116. Lee GD, et al. J Thorac Oncol (2017) PMID: 28502721
117. Gow CH, et al. Lung Cancer (2017) PMID: 28024701
118. J. Clin. Oncol. (2011) PMID: 22042966
119. Jung KH, et al. Arch. Pharm. Res. (2012) PMID: 22553051
120. Kong-Beltran M, et al. Cancer Res. (2006) PMID: 16397241
121. Onozato R, et al. J Thorac Oncol (2009) PMID: 19096300
122. Okuda K, et al. Cancer Sci. (2008) PMID: 19037978
123. Awad MM, et al. J. Clin. Oncol. (2016) PMID: 26729443
124. Gray MJ, et al. Am. J. Hum. Genet. (2015) PMID: 26637977
125. Peschard P, et al. J. Biol. Chem. (2004) PMID: 15123609
126. Lee JM, et al. Oncogene (2014) PMID: 23208509
127. Lee JH, et al. Exp. Mol. Med. (2006) PMID: 17079873
128. Togashi Y, et al. Lung Cancer (2015) PMID: 26547802
129. Peschard P, et al. Mol. Cell (2001) PMID: 11741535
130. Abella JV, et al. Mol. Cell. Biol. (2005) PMID: 16227611
131. Drilon et al., 2018; WCLC Abstract OA12.02
132. Felip et al., 2018; WCLC Abstract OA12.01
133. Wolf et al., 2018; ESMO Abstract LBA52
134. Moro-Sibilot et al., 2018; WCLC Abstract OA12.03
135. Berry ZS, et al. JAMA (1993) PMID: 8315738
136. Robert C, et al. N. Engl. J. Med. (2015) PMID: 25399552
137. Weber JS, et al. Lancet Oncol. (2015) PMID: 25795410
138. Larkin J, et al. N. Engl. J. Med. (2015) PMID: 26027431
139. Postow MA, et al. N. Engl. J. Med. (2015) PMID: 25891304
140. Topalian SL, et al. J. Clin. Oncol. (2014) PMID: 24590637
141. Brahmer J, et al. N. Engl. J. Med. (2015) PMID: 26028407
142. Borghaei H, et al. N. Engl. J. Med. (2015) PMID: 26412456
143. Rizvi NA, et al. Lancet Oncol. (2015) PMID: 25704439
144. Motzer RJ, et al. N. Engl. J. Med. (2015) PMID: 26406148
145. Schmid et al., 2016; ASCO Abstract 11506
146. Verstovsek S, et al. Br. J. Haematol. (2013) PMID: 23480528
147. Zhang Y, et al. Onco Targets Ther (2014) PMID: 24748806
148. Kim MY, et al. Lung Cancer (2015) PMID: 25662388
149. Twa DD, et al. Blood (2014) PMID: 24497532
150. Shi M, et al. Am. J. Surg. Pathol. (2014) PMID: 25025450
151. Romer JT, et al. Cancer Cell (2004) PMID: 15380514
152. Berman DM, et al. Science (2002) PMID: 12202832
153. Amakye D, et al. Nat. Med. (2013) PMID: 24202394
154. Geyer N, et al. Front Oncol (2018) PMID: 30319965
155. Shou Y, et al. Clin. Cancer Res. (2015) PMID: 25473003
156. Von Hoff DD, et al. N. Engl. J. Med. (2009) PMID: 19726763
157. Rudin CM, et al. N. Engl. J. Med. (2009) PMID: 19726761
158. Robinson GW, et al. J. Clin. Oncol. (2015) PMID: 26169613
159. Tang Y, et al. Nat. Med. (2014) PMID: 24973920
160. Gialmanidis IP, et al. Lung Cancer (2009) PMID:

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19200615
161. Zhao Y, et al. Clin Lung Cancer (2011) PMID: 21889114
162. Taipale J, et al. Nature (2002) PMID: 12192414
163. Stone DM, et al. Nature (1996) PMID: 8906787
164. Stanton BZ, et al. Mol Biosyst (2010) PMID: 20024066
165. Johnson RL, et al. Science (1996) PMID: 8658145
166. Hahn H, et al. Cell (1996) PMID: 8681379
167. Nieuwenhuis E, et al. Dev. Biol. (2007) PMID: 17631878
168. Harvey MC, et al. J. Biol. Chem. (2014) PMID: 24570001
169. Thibert C, et al. Science (2003) PMID: 12907805
170. Mille F, et al. Nat. Cell Biol. (2009) PMID: 19465923
171. Konecny GE, et al. Clin. Cancer Res. (2011) PMID: 21278246
172. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) PMID: 21871868
173. Cen L, et al. Neuro-oncology (2012) PMID: 22711607
174. Logan JE, et al. Anticancer Res. (2013) PMID: 23898052
175. Elvin JA, et al. Oncologist (2017) PMID: 28283584
176. Gao J, et al. Curr Oncol (2015) PMID: 26715889
177. Gopalan et al., 2014; ASCO Abstract 8077
178. Peguero et al., 2016; ASCO Abstract 2528
179. Konecny et al., 2016; ASCO Abstract 5557
180. DeMichele A, et al. Clin. Cancer Res. (2015) PMID: 25501126
181. Finn RS, et al. Lancet Oncol. (2015) PMID: 25524798
182. Infante JR, et al. Clin. Cancer Res. (2016) PMID: 27542767
183. Johnson DB, et al. Oncologist (2014) PMID: 24797823
184. Van Maerken T, et al. Mol. Cancer Ther. (2011) PMID: 21460101
185. Gamble LD, et al. Oncogene (2012) PMID: 21725357
186. Doxtader EE, et al. Hum. Pathol. (2012) PMID: 21840041
187. Gazzeri S, et al. Oncogene (1998) PMID: 9484839
188. Kratzke RA, et al. Cancer Res. (1996) PMID: 8758904
189. Lee JU, et al. Tuberc Respir Dis (Seoul) (2012) PMID: 23101020
190. Cortot AB, et al. Clin Lung Cancer (2014) PMID: 24169260
191. Mounawar M, et al. Cancer Res. (2007) PMID: 17575133
192. Kawabuchi B, et al. Int. J. Cancer (1999) PMID: 9988232
193. Xing XB, et al. PLoS ONE (2013) PMID: 23805242
194. Lou-Qian Z, et al. PLoS ONE (2013) PMID: 23372805
195. Quelle DE, et al. Cell (1995) PMID: 8521522
196. Mutat. Res. (2005) PMID: 15878778
197. Oncogene (1999) PMID: 10498883
198. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) PMID: 16869746
199. Ozenne P, et al. Int. J. Cancer (2010) PMID: 20549699
200. Ruas M, et al. Oncogene (1999) PMID: 10498896
201. Jones R, et al. Cancer Res. (2007) PMID: 17909018
202. Haferkamp S, et al. Aging Cell (2008) PMID: 18843795
203. Huot TJ, et al. Mol. Cell. Biol. (2002) PMID: 12417717
204. Rizos H, et al. J. Biol. Chem. (2001) PMID: 11518711
205. Gombart AF, et al. Leukemia (1997) PMID: 9324288
206. Yang R, et al. Cancer Res. (1995) PMID: 7780957
207. Parry D, et al. Mol. Cell. Biol. (1996) PMID: 8668202
208. Greenblatt MS, et al. Oncogene (2003) PMID: 12606942
209. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) PMID: 10491434
210. Poi MJ, et al. Mol. Carcinog. (2001) PMID: 11255261
211. Byeon IJ, et al. Mol. Cell (1998) PMID: 9660926
212. Kannengiesser C, et al. Hum. Mutat. (2009) PMID: 19260062
213. Lal G, et al. Genes Chromosomes Cancer (2000) PMID: 10719365
214. Koh J, et al. Nature (1995) PMID: 7777061
215. McKenzie HA, et al. Hum. Mutat. (2010) PMID: 20340136
216. Miller PJ, et al. Hum. Mutat. (2011) PMID: 21462282
217. Kutscher CL, et al. Physiol. Behav. (1977) PMID: 905385
218. Scaini MC, et al. Hum. Mutat. (2014) PMID: 24659262
219. Jenkins NC, et al. J. Invest. Dermatol. (2013) PMID: 23190892
220. Walker GJ, et al. Int. J. Cancer (1999) PMID: 10389768
221. Rutter JL, et al. Oncogene (2003) PMID: 12853981
222. Itahana K, et al. Cancer Cell (2008) PMID: 18538737
223. Zhang Y, et al. Mol. Cell (1999) PMID: 10360174
224. Zhang Y, et al. Cell (1998) PMID: 9529249
225. Gewinner C, et al. Cancer Cell (2009) PMID: 19647222
226. Fedele CG, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) PMID: 21127264
227. Yuen JW, et al. PLoS ONE (2014) PMID: 25126743
228. Lundin C, et al. Genes Chromosomes Cancer (2012) PMID: 22072402
229. Hodgson MC, et al. Cancer Res. (2011) PMID: 21224358
230. Stjernström A, et al. Cancer Med (2014) PMID: 24500884
231. Agoulnik IU, et al. Oncotarget (2011) PMID: 21487159
232. Bertucci MC, et al. Ann. N. Y. Acad. Sci. (2013) PMID: 23551093
233. Geissler et al., 2015; EHA Abstract E1347
234. Deisseroth A, et al. Clin. Cancer Res. (2012) PMID: 22544377
235. Verstovsek S, et al. Blood (2012) PMID: 22718840
236. Barosi G, et al. Leukemia (2016) PMID: 26975727
237. Pardanani A, et al. JAMA Oncol (2015) PMID: 26181658
238. Harrison CN, et al. Lancet Haematol (2017) PMID: 28602585
239. Gao SM, et al. Exp. Hematol. (2013) PMID: 23111066
240. Novotny-Diermayr V, et al. Blood Cancer J (2012) PMID: 22829971
241. Xiong H, et al. Mol. Carcinog. (2012) PMID: 21520296
242. Rambaldi A, et al. Leukemia (2020) PMID: 32047238
243. Schwaab J, et al. Ann. Hematol. (2015) PMID: 25260694
244. Rumi E, et al. Ann. Hematol. (2015) PMID: 26202607
245. Rumi E, et al. J. Clin. Oncol. (2013) PMID: 23630205
246. Lierman E, et al. Blood (2012) PMID: 22899477
247. Chase A, et al. Haematologica (2013) PMID: 22875628
248. Schinnerl D, et al. Blood (2015) PMID: 25515960
249. Roberts KG, et al. N. Engl. J. Med. (2014) PMID: 25207766
250. Doudican et al., 2015; AACR Abstract 5443
251. Hao Y, et al. Clin. Cancer Res. (2014) PMID: 24610827
252. Bhagwat N, et al. Blood (2014) PMID: 24470592
253. Weigert O, et al. J. Exp. Med. (2012) PMID: 22271575
254. Looyenga BD, et al. PLoS ONE (2012) PMID: 22319590
255. Zhao M, et al. Lung Cancer (2011) PMID: 21333372
256. Jatiani SS, et al. Genes Cancer (2010) PMID: 21442038
257. Herbst RS, et al. Clin. Cancer Res. (2015) PMID: 25680375
258. Jotte R, et al. J Thorac Oncol (2020) PMID: 32302702
259. Socinski MA, et al. N. Engl. J. Med. (2018) PMID: 29863955
260. West H, et al. Lancet Oncol. (2019) PMID: 31122901
261. Barlesi et al., 2018; ESMO Abstract LBA54
262. Spigel et al., 2019; ESMO Abstract LBA78
263. Rittmeyer A, et al. Lancet (2017) PMID: 27979383
264. Smith et al., 2016; ASCO Abstract 9028
265. Pietras et al., 2018; WCLC Abstract P1.04-3
266. Wolf et al., 2019; ASCO Abstract 9004
267. Schuler et al., 2016; ASCO Abstract 9067
268. Riedel et al., 2019; ASCO abstract 9030
269. van den Bent M, et al. J. Neurooncol. (2020) PMID: 31776899
270. Bang YJ, et al. Cancer Sci. (2020) PMID: 31778267
271. Esaki T, et al. Cancer Sci. (2019) PMID: 30724423
272. Vassal et al., 2015; ASCO Abstract 2595
273. Li et al., 2015; ASCO Abstract 8090
274. Ou SH, et al. J Thorac Oncol (2011) PMID: 21623265
275. Schwab R, et al. Lung Cancer (2014) PMID: 24192513
276. Le X, et al. Clin Lung Cancer (2015) PMID: 25922291
277. Ali SM, et al. Oncologist (2015) PMID: 25882375
278. Lennerz JK, et al. J. Clin. Oncol. (2011) PMID: 22042947
279. Chi AS, et al. J. Clin. Oncol. (2012) PMID: 22162573
280. Palma NA, et al. Case Rep Oncol (2014) PMID: 25232318
281. Benderra MA, et al. J Thorac Oncol (2016) PMID: 26845121
282. Drilon A, et al. Nat. Med. (2020) PMID: 31932802
283. Landi L, et al. Clin. Cancer Res. (2019) PMID: 31416808
284. Moro-Sibilot D, et al. Ann. Oncol. (2019) PMID: 31584608
285. Awad MM, et al. Lung Cancer (2019) PMID: 31200835
286. Shaw et al., 2016; ASCO Abstract 9066
287. Lu et al., 2016; ASCO Abstract 9058
288. Yoshida T, et al. J. Clin. Oncol. (2016) PMID: 27354483
289. Solomon BJ, et al. N. Engl. J. Med. (2014) PMID: 25470694
290. Shaw AT, et al. N. Engl. J. Med. (2013) PMID: 23724913
291. Goto et al., 2016; ASCO Abstract 9022
292. Shaw AT, et al. N. Engl. J. Med. (2014) PMID: 25264305
293. Mazières J, et al. J. Clin. Oncol. (2015) PMID: 25667280
294. Scheffler M, et al. Oncotarget (2015) PMID: 25868855
295. Vaishnavi A, et al. Nat. Med. (2013) PMID: 24162815
296. Drilon et al., 2016; ASCO Abstract 108
297. Camidge et al., 2014; ASCO Abstract 8001
298. Schrock AB, et al. J Thorac Oncol (2016) PMID: 27343443
299. Jorge SE, et al. Lung Cancer (2015) PMID: 26791794
300. Mahjoubi L, et al. Invest New Drugs (2016) PMID: 26892698
301. Zhang Y, et al. J Thorac Oncol (2016) PMID: 26724472
302. Disis et al., 2016; ASCO Abstract 5533
303. Dirix et al., 2016; SABCS Abstract S1-04
304. Verschraegen et al., 2016; ASCO Abstract 9036
305. Gulley et al., 2015; ECC Abstract 3090
306. Antonia SJ, et al. N. Engl. J. Med. (2018) PMID: 30280658
307. Gray JE, et al. J Thorac Oncol (2020) PMID: 31622733
308. Cho et al., 2019; ELCC Abstract LBA3
309. Kowalski et al., 2018; ESMO Abstract 1378O
310. Antonia SJ, et al. J Thorac Oncol (2019) PMID: 31228626
311. Garassino MC, et al. Lancet Oncol. (2018) PMID: 29545095
312. Garassino et al., 2018; WCLC Abstract P1.01-21
313. Govindan et al., 2017; DOI: 10.1016/j.jtho.2017.09.534
314. Chaft et al., 2018; AACR Abstract CT113
315. Topalian SL, et al. N. Engl. J. Med. (2012) PMID: 22658127
316. Lind et al., 2020; BTOG Abstract 113
317. Paz-Ares et al., 2019; ESMO Immuno-Oncology Congress Abstract LBA3
318. Rizvi NA, et al. J. Clin. Oncol. (2016) PMID: 27354481
319. Godfrey J, et al. Blood (2019) PMID: 30910787
320. Mok TSK, et al. Lancet (2019) PMID: 30955977
321. Reck M, et al. J. Clin. Oncol. (2019) PMID: 30620668
322. Herbst RS, et al. Lancet (2016) PMID: 26712084
323. Garon EB, et al. J. Clin. Oncol. (2019) PMID: 31154919
324. Aguilar EJ, et al. Ann. Oncol. (2019) PMID: 31435660
325. Gadgeel S, et al. J. Clin. Oncol. (2020) PMID: 32150489
326. Paz-Ares L, et al. N. Engl. J. Med. (2018) PMID: 30280635

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327. Doherty et al., 2018; WCLC Abstract P1.01-16
328. Powell et al., 2019; ESMO Abstract 1483PD
329. Mansfield et al., 2019; ESMO Abstract 1482O
330. Goldberg SB, et al. Lancet Oncol. (2016) PMID: 27267608
331. Gubens MA, et al. Lung Cancer (2019) PMID: 30885353
332. Gray JE, et al. Clin. Cancer Res. (2019) PMID: 31409616
333. Brose et al., 2019; doi:10.1200/JCO.2019.37.8_suppl.16
334. Gulley JL, et al. Lancet Oncol. (2017) PMID: 28373005
335. Klempner SJ, et al. J Thorac Oncol (2017) PMID: 27693535
336. Yakes FM, et al. Mol. Cancer Ther. (2011) PMID: 21926191
337. Weber H, et al. J Biomol Screen (2014) PMID: 25260782
338. Navis AC, et al. PLoS ONE (2013) PMID: 23484006
339. Yeh I, et al. Nat Commun (2015) PMID: 26013381
340. Lee YH, et al. Cancers (Basel) (2014) PMID: 25534569
341. Torres KE, et al. Clin. Cancer Res. (2011) PMID: 21540237
342. Sameni M, et al. Clin. Cancer Res. (2016) PMID: 26432786
343. Hellerstedt BA, et al. Clin Lung Cancer (2019) PMID: 30528315
344. Neal JW, et al. Lancet Oncol. (2016) PMID: 27825638
345. Nokihara H, et al. Clin Lung Cancer (2019) PMID: 30718102
346. Garon EB, et al. N. Engl. J. Med. (2015) PMID: 25891174
347. Bellone S, et al. Clin. Cancer Res. (2018) PMID: 29351920
348. Moreno et al., 2018; WCLC Abstract MA04.01
349. Rodon J, et al. Clin. Cancer Res. (2014) PMID: 24523439
350. Migden MR, et al. Lancet Oncol. (2015) PMID: 25981810
351. Dummer R, et al. Br. J. Dermatol. (2019) PMID: 31545507
352. Stathis A, et al. Invest New Drugs (2017) PMID: 28317088
353. Sekulic A, et al. N. Engl. J. Med. (2012) PMID: 22670903
354. LoRusso PM, et al. Clin. Cancer Res. (2011) PMID: 21300762
355. Gajjar A, et al. Clin. Cancer Res. (2013) PMID: 24077351
356. Lorusso PM, et al. Clin. Cancer Res. (2011) PMID: 21753154

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