FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Wang, I Fei	Lung adenocarcinoma	11 Jan 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1537940-01

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

PATIENT
DISEASE Lung adenocarcinoma
NAME Wang, I Fei
DATE OF BIRTH 21 October 1973
SEX Female
MEDICAL RECORD # 25706121

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Lung
SPECIMEN ID S111-54088 A (PF23003)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 23 December 2022
SPECIMEN RECEIVED 05 January 2023

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.

EGFR L858R
APC E1295* - subclonal†
PIK3CA G118D, M1004I - subclonal†
PTEN loss exons 1-2
RB1 loss exons 14-27

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

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Afatinib** (p. 7), **Dacomitinib** (p. 8), **Erlotinib** (p. 8), **Gefitinib** (p. 9), **Osimertinib** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
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

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

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
EGFR - L858R	Afatinib 1	none
	Dacomitinib 1	
	Erlotinib 1	
	Gefitinib 1	
10 Trials see p. 12	Osimertinib 1	
APC - E1295* - subclonal	none	none
2 Trials see p. 11		
PIK3CA - G118D, M1004I - subclonal	none	none
10 Trials see p. 14		
PTEN - loss exons 1-2	none	none
10 Trials see p. 16		

☐ *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.

RB1 - loss exons 14-27 ..... p. 6

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

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[6]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2022).

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

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others);[22-23,26-28,32-39]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[40], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[41], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[42]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[43]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[44-45], several other large studies did find a strong association with increased TMB[46-49]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[50]. A meta-analysis of 19 studies of immune checkpoint inhibitor-treated NSCLC (n = 2,315 patients) demonstrated that high TMB predicted a significantly longer OS than low TMB (HR = 0.70), and within the high TMB group, immunotherapy was associated with an improved PFS (HR = 0.62, P<0.001), OS (HR = 0.67, P<0.001) and a higher response rate (OR = 2.35, P<0.001) compared to chemotherapy[51]. In contrast, a large study of Chinese patients with untreated lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[44]. Another study of patients with NSCLC treated with EGFR inhibitors or platinum doublet chemotherapy found elevated TMB to be correlated with poorer prognosis, as well as finding lower TMB in combination with PD-L1 negative status to be significantly associated with longer median survival in patients with lung adenocarcinoma[52]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[52-53].

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[54-55] and cigarette smoke in lung cancer[32,56], treatment with temozolomide-based chemotherapy in glioma[57-58], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[59-63], and microsatellite instability (MSI)[59,62-63]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[22-23,26-28,32-39,64].

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GENE
EGFR

ALTERATION
L858R

TRANSCRIPT ID
NM_005228.3

CODING SEQUENCE EFFECT
2573T>G

VARIANT CHROMOSOMAL POSITION
chr7:55259515

VARIANT ALLELE FREQUENCY (% VAF)
28.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer (NSCLC), EGFR activating mutations may predict sensitivity to EGFR-TKIs, including erlotinib[65], gefitinib[66-69], afatinib[70-73], dacomitinib[74], and osimertinib[71,75]; however, the data for patients with other tumor types are limited[76-81]. A Phase 1 study of amivantamab monotherapy or amivantamab in combination with lazertinib for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) has produced encouraging preliminary results for treatment-naive patients and patients who relapsed after treatment with osimertinib with and without chemotherapy, including osimertinib-relapsed patients with biomarkers indicating EGFR/MET-based osimertinib resistance[82-84]. For patients with EGFR exon 18-mutated pretreated NSCLC, the updated results from the SUMMIT basket trial of neratinib reported an ORR of 34% (10/29) and median PFS of 5.8 months, including ORRs of 30% (7/23) for TKI-pretreated patients, 50% (3/6) for TKI-naive patients, and 29% (2/7) for those with brain metastases[85]. A Phase 1 study showed that the MET antibody-drug conjugate telisotuzumab vedotin (teliso-V) plus osimertinib yielded an ORR of 58% (11/19) for patients with EGFR-mutated, MET-overexpressing NSCLC who progressed on osimertinib, including ORRs of 56% (5/9) for patients with EGFR L858R mutation and 67% (6/9) for those with EGFR exon 19 deletion and no response for a patient with EGFR G719S mutation[86]. In a Phase 1 trial, the HER3-targeted antibody patritumab deruxtecan elicited an ORR of 39% (22/57, 1 CR) and a median PFS of 8.2 months for patients with non-small cell lung cancer previously treated with an EGFR TKI, many of whom displayed TKI resistance alterations[87]. A Phase 1 trial evaluating the EGFR inhibitor AZD3759 reported a reduction in the volume of brain metastases in 40% (8/20) of patients with previously treated non-small cell lung cancer (NSCLC) harboring either the EGFR L858R alteration or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[88-89]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54% (69/127) for all evaluable patients and 44% (8/18, intracranial) for patients with brain metastases[90]. A Phase 1 trial evaluating the irreversible pan-HER inhibitor FCN-411 for NSCLC patients who had EGFR mutations and experienced disease progression on standard treatments reported an ORR of 15% with 10/67 patients achieving PR, and a DCR of 73% with 39 additional patients achieving SD[91]. OR was observed in a numerically higher proportion of patients with the EGFR T790M mutation than those without this mutation[91]. The Phase 3 AENEAS trial of first-line aumolertinib, a third-generation EGFR TKI, for patients with locally advanced or metastatic NSCLC harboring either the EGFR L858R alteration or EGFR exon 19 deletion reported significantly improved mPFS (19.3 months vs. 9.9 months) and similar ORR (74% vs. 72%) and DCR (93% vs. 97%) compared with gefitinib[92].

— Potential Resistance —

For patients with NSCLC treated with EGFR tyrosine kinase inhibitors, PIK3CA mutation is associated with shorter OS in a meta-analysis (pooled HR of 1.83)[93]. Clinical studies of lung cancer have shown that acquired PIK3CA mutation may confer resistance to EGFR inhibitors like osimertinib[94].

— Nontargeted Approaches —

Patients with EGFR-mutated non-squamous metastatic non-small cell lung cancer (NSCLC) who progressed on EGFR TKI have benefited from immune checkpoint inhibitors combined with antiangiogenic therapy and chemotherapy, particularly atezolizumab plus bevacizumab plus carboplatin and paclitaxel (OS HR=0.61 compared with bevacizumab/chemotherapy)[95-97] or sintilimab plus bevacizumab biosimilar IBI305 plus cisplatin and pemetrexed (PFS HR=0.46 compared with chemotherapy alone)[98].

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[48,99-100] and in 4% of lung squamous cell carcinomas[101]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[102-107]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[108-109]. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[110-111]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[112] or resected Stage 1 NSCLC[113].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[114]. EGFR L858 is located in the kinase domain and is encoded by exon 21. EGFR L858R has been characterized as activating[115-117] and patients with the L858R mutation have been shown to be sensitive to EGFR tyrosine kinase inhibitors, such as erlotinib, gefitinib[115-117], and afatinib[118].

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GENE
APC

ALTERATION
E1295* - subclonal

TRANSCRIPT ID
NM_000038.4

CODING SEQUENCE EFFECT
3883G>T

VARIANT CHROMOSOMAL POSITION
chr5:112175174

VARIANT ALLELE FREQUENCY (% VAF)
2.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs[119], and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP[120-121]. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days[122]; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386[123-124].

FREQUENCY & PROGNOSIS

APC mutations have been reported in 1.7%-4.3% of lung adenocarcinomas[47-48,100] and in 1.1% of lung squamous cell carcinomas (SCCs)[101]. In contrast, loss of heterozygosity (LOH) at the APC/MCC locus has been reported in up to 68% (17/25) of non-small cell lung cancers (NSCLCs), with a higher incidence in SCCs compared with adenocarcinomas[125-126]. Hypermethylation of APC in NSCLC tumors has been reported in a number of studies[127-130]; hypermethylation and lower APC mRNA expression have been associated with poorer survival in patients with NSCLC[126,131]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[132].

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[133]. Alterations such as seen here may disrupt APC function or expression[134-138].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[139-141]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[142], and in the appropriate clinical context germline testing of APC is recommended.

GENE
PIK3CA

ALTERATION
G118D, M1004I - subclonal

TRANSCRIPT ID
NM_006218.2, NM_006218.2

CODING SEQUENCE EFFECT
353G>A, 3012G>A

VARIANT CHROMOSOMAL POSITION
chr3:178917478, chr3:178951957

VARIANT ALLELE FREQUENCY (% VAF)
41.0%, 4.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[143-150], AKT[151-152], or mTOR[153-160]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[150]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[149]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[147-148]. A Phase 2 study of buparlisib in NSCLC observed 2 PRs (3.2%; 2/63) in PIK3CA-pathway activated tumors, although the study did not meet its primary endpoint[161].

— Potential Resistance —

For patients with NSCLC treated with EGFR tyrosine kinase inhibitors, PIK3CA mutation is associated with shorter OS in a meta-analysis (pooled HR of 1.83)[93]. Clinical studies of lung cancer have shown that acquired PIK3CA mutation may confer resistance to EGFR inhibitors like osimertinib[94].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3CA mutation was observed in 8.2% of lung adenocarcinoma cases[162] and in 15.7% of lung squamous cell carcinoma cases[101]. The prognostic significance of PIK3CA mutation or overexpression in NSCLC is unclear, with several studies reporting contradictory data, which may be influenced by the specific PIK3CA mutation, histologic subtype, and the presence of concurrent mutations in oncogenes such as EGFR and KRAS[163-168].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[169-170]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[171-192]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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GENE
PTEN

ALTERATION
loss exons 1-2

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[148,193-195]. Across various tissues, most clinical studies have not observed an association between PTEN deficiency and response to inhibitors of the PI3K-AKT-mTOR pathway. However, limited studies in prostate cancer[196-199], renal cell carcinoma[200], breast cancer[201-202], and colorectal cancer[203] have reported an association between PTEN deficiency and response to inhibitors targeting the PI3K-AKT-mTOR pathway. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[204-208], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[209], ovarian cancer[210], uterine leiomyosarcoma[211], and endometrial cancer[208] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[212-213].

FREQUENCY & PROGNOSIS

Studies have reported PTEN mutations in 6.7% (12/178) to 10% (6/59) of lung squamous cell carcinomas[101,214] but less frequently in lung adenocarcinomas (1.1-2.2%)[36,47-48,100,214]. Loss of PTEN expression by IHC was reported in up to 35% of NSCLC cases in one study, with several studies reporting more frequent loss of PTEN in squamous cell lung carcinoma compared to lung adenocarcinoma[215-218]. Loss of PTEN protein expression has been identified as a marker of poor prognosis in NSCLC[215,217].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[194]. Alterations such as seen here may disrupt PTEN function or expression[219-260].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[261-262]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[261,263]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[261]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
RB1

ALTERATION
loss exons 14-27

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data[264] and strong preclinical data[265-268], RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer (SCLC). A clinical study evaluating the Aurora kinase A inhibitor alisertib for patients with prostate cancer did not find an association between RB1 deletion and clinical benefit[269]. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members[270] and activation of the NOTCH pathway[271].

FREQUENCY & PROGNOSIS

RB1 mutations have been reported in 4.5% of lung squamous cell carcinoma (SCC) cases[101] and 3.5% of lung adenocarcinoma cases[100]. One study found that RB1 expression was correlated with poor prognosis for patients with NSCLC[272].

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[273-274]. Alterations such as seen here may disrupt RB1 function or expression[275-281].

POTENTIAL GERMLINE IMPLICATIONS

Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[282]. Germline mutations in RB1 account for approximately 40% of RB tumors[283] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[284-285]. In the appropriate clinical context, germline testing of RB1 is recommended.

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Afatinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[70,74,286-287] , whereas data for patients with other tumor types are limited[76-81,288] .

SUPPORTING DATA

In the first-line setting for patients who are EGFR TKI naive with non-small cell lung cancer (NSCLC) harboring common EGFR mutations (exon 19 or L858R alterations), afatinib has shown improved clinical benefit and responses as compared with chemotherapy in the Phase 3 LUX-Lung 3 and LUX-Lung 6 trials[70,286] and to gefitinib in the Phase 2b LUX-Lung 7 trial[289-290] ; these outcomes are supported in additional prospective or randomized Phase 2 trials[291-292] . Alteration-specific differences in OS response have also been reported in patients who are treatment naive, with increased OS observed in patients with EGFR exon 19 alterations between afatinib and comparator arms versus no significant OS differences for patients with L858R mutations in the same treatment settings[118,293] . In the second-line setting, patients with metastatic NSCLC and common EGFR mutations who progressed on prior chemotherapy experienced an ORR of 50% (30/60) from afatinib in a Phase 4 trial[294]. A retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 27% for patients with common sensitizing EGFR mutations and an ORR of 24% for the entire cohort[295]. In a case report, a patient with NSCLC with exon 19 deletion and leptomeningeal metastases experienced an ongoing 16-month PR from afatinib in extracranial, brain, and leptomeningeal lesions[296]. For patients with erlotinib- or gefitinib-resistant NSCLC and EGFR mutations, Phase 2/3 studies of afatinib treatment have generally reported ORRs of only 7 to 9%[297-302] ; however, DCRs of more than 50% have been observed[301]. In a Phase 1b or observational study, patients with EGFR-mutated NSCLC who progressed on afatinib experienced further clinical benefit from subsequent treatment with afatinib and cetuximab[303] or osimertinib[304], respectively. In the LUX-Lung 1 Phase 2b/3 trial for patients with advanced non-small cell lung cancer (NSCLC) who previously progressed on first-generation EGFR tyrosine kinase inhibitors, afatinib treatment resulted in longer median PFS (mPFS; 3.3 vs. 1.1 months, HR=0.38) but no significant difference in median OS (mOS; 10.8 vs. 12.0 months, HR=1.08) when compared with placebo[297]; similar results were observed in the single-arm LUX-Lung 4 trial in the same treatment setting[299]. The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer mOS (7.9 vs. 6.8 months, HR=0.81), significantly longer mPFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[305]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[306].

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Dacomitinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[70,74,286-287] , whereas data for patients with other tumor types are limited[76-81,288] . Patients with untreated advanced NSCLC and EGFR L858R mutations achieved an ORR of 73% (68/93)[307] and a median OS of 32.5 months with dacomitinib[74].

SUPPORTING DATA

A randomized Phase 3 trial for patients with non-small cell lung cancer (NSCLC) harboring activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS [mOS] of 34.1 vs. 26.8 months, HR=0.760; median PFS [mPFS] of 14.7 vs. 9.2 months, HR=0.59)[307-308] ; mOS was 34.1 to 36.7 months and ORR was 75% to 79%, depending on the dosing regimen[309]. A pooled subgroup analysis for patients with NSCLC harboring activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (mPFS of 14.6 vs. 9.6 months, HR=0.717; mOS of 26.6 vs. 23.2 months, HR=0.737)[310]. An analysis of dacomitinib in NSCLC comparing common activating EGFR alterations alone with co-occurring common and uncommon EGFR mutations showed no statistically significant difference in total ORR (33% vs. 40%, p=0.636) or DCR (77% vs. 73%, p=0.089); however, multivariate analysis revealed compound mutation status as an independent predictor of worse OS (HR=5.405)[311]. A Phase 1 trial of combination dacomitinib and a MEK1/2 inhibitor for patients with KRAS-mutated CRC, NSCLC, or pancreatic cancer reported 20/36 SDs and 16 PDs, however toxicity from this combination prevented long-term treatment in this patient population[312]. Phase 1/2 studies of dacomitinib for patients with advanced KRAS-wildtype non-small cell lung cancer (NSCLC) who had previously progressed on chemotherapy and erlotinib or gefitinib and were not selected for EGFR mutations reported ORRs of 4.6-17% (3/66-9/53), median PFS of 3-4 months, and median OS of 9-11 months[313-314] .

Erlotinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[65,315-317] .

SUPPORTING DATA

For patients with EGFR-mutated non-small cell lung cancer (NSCLC), the Phase 3 EURTAC trial improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37), though OS was not prolonged (22.9 vs 19.6 months, HR=0.92)[65,318] . This study and meta-analyses attribute the lack of OS benefit to the effectiveness of post-progression salvage therapy in the control arm[319]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[320]. Patients with EGFR-mutated NSCLC have experienced PFS benefit with the addition of bevacizumab to erlotinib in the first-line setting in Phase 3 trials including the ARTEMIS-CTONG1509 trial for Chinese patients (17.9 vs. 11.2 months, HR=0.55)[321], the NEJ026 trial for Japanese patients (16.9 vs. 13.3 months, HR=0.605)[322-323] , and the international BEVERLY trial (15.4 vs. 9.7 months, HR=0.60)[324]; OS benefit has not been observed across these studies. In the maintenance setting, Phase 3 trials have reported significantly improved PFS with maintenance erlotinib following first-line platinum-based chemotherapy, with the largest benefit for patients with EGFR mutations[315,325] . In the neoadjuvant setting, a Phase 2 trial reported a numerically improved ORR and significantly longer PFS with erlotinib compared with chemotherapy for patients with EGFR-mutated advanced NSCLC[316]. In the placebo-controlled Phase 3 RELAY trial, the addition of ramucirumab to erlotinib improved PFS for previously untreated patients with NSCLC harboring EGFR L858R or exon 19 deletion (19.4 vs. 12.4 months, HR=0.59)[326].

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Gefitinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[317,327-332] , and responses have been reported for patients with EGFR-rearranged NSCLC[333-334] .

SUPPORTING DATA

Gefitinib achieved an ORR of 69.8% and OS of 19.2 months as first-line treatment for Caucasian patients with non-small cell lung cancer (NSCLC) and EGFR sensitizing mutations[66]. Phase 3 studies for Japanese patients[329,335] and East Asian patients[330,336] with EGFR-mutated NSCLC reported longer PFS but not longer OS on first-line gefitinib compared with cisplatin and docetaxel or carboplatin and paclitaxel. Retrospective analysis of East Asian patients receiving first-line gefitinib reported greatest PFS benefit among patients with EGFR exon 19 insertions or deletions and shortest PFS for those with exon 20 insertions (1.2 months)[337]. Two Phase 3 trials of the combination gefitinib plus pemetrexed and carboplatin compared with gefitinib alone for patients with advanced NSCLC harboring EGFR activating mutations reported significantly higher ORRs (75.3% and 84% vs. 62.5% and 67%), longer median PFS (16 and 20.9 months vs. 8 and 11.9 months), and longer median OS (50.9 months and not reached vs. 17 and 38.8 months) with combination treatment; however, combination treatment was associated with increased Grade 3 or higher adverse events[338-339] . In a Phase 1 study for treatment-naive patients with NSCLC, 63% (19/30) of patients experienced PR from the combination of gefitinib and the PD-L1 inhibitor durvalumab[340].

Osimertinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR TKI that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved in various treatment settings for patients with non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions, exon 21 L858R mutations, or T790M mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations or rearrangements and/or the EGFR T790M mutation may predict sensitivity to osimertinib in non-small cell lung cancer[75,333,341-343] . Patients with untreated advanced NSCLC and EGFR exon 19 deletions or L858R mutations achieved an ORR of 80% and a median PFS of 21.4 and 14.4 months, respectively[341].

SUPPORTING DATA

The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (mPFS; 18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months; HR=0.80) for patients with advanced non-small cell lung cancer (NSCLC) and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858)[341,344] . In the Phase 3 ADAURA study, patients with early-stage (IB/II/IIIA) EGFR-mutated NSCLC experienced longer disease-free survival on osimertinib compared with placebo in the adjuvant setting (65.8 vs. 28.1 months, HR=0.27)[345]. A Phase 1 study reported that T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and a median PFS of 2.8 months[75]. A Phase 1b/2 study evaluating osimertinib in combination with the CD73 inhibitor oleclumab for patients with advanced EGFR-mutated, T790M-negative NSCLC reported an ORR of 19% (4/21), a DCR of 81%, and mPFS of 11 months (Kim et al., 2021 AACR Abstract CT163). A Phase 2 trial of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with untreated advanced non-small cell lung cancer (NSCLC) harboring EGFR del19 or L858R reported no difference in ORR (82% vs 86%) and median PFS (22.1 vs 20.2 months, HR 0.862 p=0.213)[346]. The Phase 2 BOOSTER study of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with advanced NSCLC with EGFR-sensitizing mutations (exon 19 del or L858R) and L790M at progression on prior EGFR TKI reported no difference in ORR (55% vs 55%), median OS (24.0 vs 24.3 months, HR 1.03 p=0.91), or median PFS (15.4 vs 12.3 months, HR 0.96 p=0.83), although improved PFS was observed for the combination in the subgroup of current or former smokers (16.5 vs 8.4, HR 0.52) while nonsmokers had no benefit (HR 1.47)[347]. The Phase 1b TATTON study of osimertinib in combination with selumetinib, savolitinib, or durvalumab for patients with previously treated EGFR-mutated NSCLC reported ORRs of 42% (15/36), 44% (8/18), and 44% (10/23), respectively[348].

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

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

GENE
APC

ALTERATION
E1295* - subclonal

RATIONALE
Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

NCT04008797

PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Kurume (Japan), Matsuyama (Japan), Seodaemun (Korea, Republic of), Osakasayama (Japan), Nagoya (Japan), Chuo-Ku (Japan), Koto-ku (Japan), Chiba (Japan), Kashiwa (Japan), Hidaka (Japan)

NCT03264664

PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS
CBP, Beta-catenin

LOCATIONS: Glasgow (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom)

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GENE
EGFR

ALTERATION
L858R

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies.

NCT05338970

PHASE 3

HERTHENA-Lung02: A Study of Patritumab Deruxtecan Versus Platinum-based Chemotherapy in Metastatic or Locally Advanced EGFRm NSCLC After Failure of EGFR TKI Therapy

TARGETS
ERBB3

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung City (Taiwan), Kumamoto (Japan), Kurume (Japan), Fukuoka (Japan), Goyang (Korea, Republic of), Cheongju-si (Korea, Republic of)

NCT05120349

PHASE 3

A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection

TARGETS
EGFR

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Shanghai (China), Suzhou (China), Nanjing (China), Yangzhou (China), Guangzhou (China)

NCT04988295

PHASE 3

A Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With Epidermal Growth Factor Receptor (EGFR)-Mutated Locally Advanced or Metastatic Non- Small Cell Lung Cancer After Osimertinib Failure

TARGETS
MET, EGFR

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Changhua (Taiwan), New Taipei City (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Linhai (China), Hangzhou (China), Shanghai (China), Hang Zhou (China)

NCT02609776

PHASE 1

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

TARGETS
MET, EGFR

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taichung (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Nanchang (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China)

NCT03974022

PHASE 1/2

Assessing an Oral EGFR Inhibitor, DZD9008 in Patients Who Have Advanced Non-small Cell Lung Cancer With EGFR or HER2 Mutation (WU-KONG1)

TARGETS
ERBB2, EGFR

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Liuying (Taiwan), Tainan (Taiwan), Cheonju (Korea, Republic of), Suwon (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang (Korea, Republic of)

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NCT04077463

PHASE 1

A Study of Lazertinib as Monotherapy or in Combination With JNJ-61186372 in Japanese Participants With Advanced Non-small Cell Lung Cancer

TARGETS
EGFR, MET

LOCATIONS: Taipei City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Hang Zhou (China), Shanghai (China), Guangzhou (China), Changsha (China), Wuhan (China), Jinan (China)

NCT04862780

PHASE 1/2

Study Targeting EGFR Resistance Mechanisms in NSCLC

TARGETS
EGFR

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Yokohama-shi (Japan), Chuo Ku (Japan), Kashiwa (Japan), Singapore (Singapore), Amsterdam (Netherlands), Sutton (United Kingdom), Villejuif (France), Toulouse (France)

NCT05215548

PHASE 2

Primary Tumor Resection With EGFR TKI for Stage IV NSCLC

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Taipei (Taiwan)

NCT04721015

PHASE 1

Study of Intravenous (IV) ABBV-637 Alone or in Combination With IV Docetaxel/Osimertinib to Assess Adverse Events and Change in Disease Activity in Adult Participants With Relapsed/Refractory (R/R) Solid Tumors

TARGETS
EGFR

LOCATIONS: Taoyuan City (Taiwan), Tainan (Taiwan), Hsinchu City (Taiwan), Kaohsiung (Taiwan), Fukuoka-shi (Japan), Seoul (Korea, Republic of), Matsuyama-shi (Japan), Goyang (Korea, Republic of), Nagoya-shi (Japan), Chuo-ku (Japan)

NCT03114319

PHASE 1

Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors

TARGETS
SHP2, EGFR

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Kobe-shi (Japan), Singapore (Singapore), Amsterdam (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Hospitalet de LLobregat (Spain), Madrid (Spain), Toronto (Canada)

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GENE
PIK3CA

ALTERATION
G118D, M1004I - subclonal

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

NCT04589845

PHASE 2

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

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

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

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NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

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GENE
PTEN

ALTERATION
loss exons 1-2

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

NCT04380636

PHASE 3

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

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Fuzhou (China), Xiamen (China), Hangzhou (China), Shanghai (China), Shangai (China), Nanchang (China), Shenzhen (China), Nanjing (China), Changsha (China), Wuhan (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

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NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Illinois, Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

NCT04972110

PHASE 1/2

Study of RP-3500 With Niraparib or Olaparib in Advanced Solid Tumors

TARGETS
PARP, ATR

LOCATIONS: Utah, Minnesota, Michigan, Connecticut, New York, Maryland, Texas

NCT04317105

PHASE 1/2

Testing the Addition of an Anti-cancer Drug, Copanlisib, to the Usual Immunotherapy (Nivolumab With or Without Ipilimumab) in Patients With Advanced Solid Cancers That Have Changes in the Following Genes: PIK3CA and PTEN

TARGETS
PD-1, CTLA-4, PI3K

LOCATIONS: Toronto (Canada), Texas, Virginia

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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.

APC S2296N	***BCL6*** E419V	***CD22*** A697T	***CDH1*** P461S
CIC P1599S	***EGFR*** A86T	***MED12*** E227*	***MEN1*** G508D
NOTCH1 I567V	***NPM1*** amplification	***PIK3CB*** L166T	***PMS2*** L56V
POLE D225N	***RET*** V292M	***SDHA*** amplification	***SGK1*** E14G

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ORDERED TEST # ORD-1537940-01

APPENDIX Genes Assayed in FoundationOne®CDx

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 or WTX)*	
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*	*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*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
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	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (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*	*MRE11 (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*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*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*
PRKN (PARK2)	*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*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*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

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

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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

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analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

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tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.4.0

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The median exon coverage for this sample is 390x

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1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Warth A, et al. Virchows Arch. (2016) pmid: 26637197
7. Ninomiya H, et al. Br. J. Cancer (2006) pmid: 16641899
8. Vanderwalde A, et al. Cancer Med (2018) pmid: 29436178
9. Zang YS, et al. Cancer Med (2019) pmid: 31270941
10. Dudley JC, et al. Clin. Cancer Res. (2016) pmid: 26880610
11. Takamochi K, et al. Lung Cancer (2017) pmid: 28676214
12. Pylkkänen L, et al. Environ. Mol. Mutagen. (1997) pmid: 9329646
13. Gonzalez R, et al. Ann. Oncol. (2000) pmid: 11061602
14. Chen XQ, et al. Nat. Med. (1996) pmid: 8782463
15. Merlo A, et al. Cancer Res. (1994) pmid: 8174113
16. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
17. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
18. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
19. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
20. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
21. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
22. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
23. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
24. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
25. Cristescu R, et al. Science (2018) pmid: 30309915
26. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
27. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
28. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
29. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
30. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
31. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
32. Rizvi NA, et al. Science (2015) pmid: 25765070
33. Colli LM, et al. Cancer Res. (2016) pmid: 27197178
34. Wang VE, et al. J Immunother Cancer (2017) pmid: 28923100
35. Carbone DP, et al. N. Engl. J. Med. (2017) pmid: 28636851
36. Rizvi H, et al. J. Clin. Oncol. (2018) pmid: 29337640
37. Forde PM, et al. N. Engl. J. Med. (2018) pmid: 29658848
38. Miao D, et al. Nat. Genet. (2018) pmid: 30150660
39. Chae YK, et al. Clin Lung Cancer (2019) pmid: 30425022
40. Paz-Ares et al., 2019; ESMO Abstract LBA80
41. Hellmann MD, et al. N. Engl. J. Med. (2019) pmid: 31562796
42. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
43. Spigel et al., 2016; ASCO Abstract 9017
44. Xiao D, et al. Oncotarget (2016) pmid: 27009843
45. Shim HS, et al. J Thorac Oncol (2015) pmid: 26200269
46. Govindan R, et al. Cell (2012) pmid: 22980976
47. Ding L, et al. Nature (2008) pmid: 18948947
48. Imielinski M, et al. Cell (2012) pmid: 22980975
49. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
50. Stein et al., 2019; DOI: 10.1200/PO.18.00376
51. Meng G, et al. PLoS One (2022) pmid: 35113949
52. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
53. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
54. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
55. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
56. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
57. Johnson BE, et al. Science (2014) pmid: 24336570
58. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
59. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
60. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
61. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
62. Nature (2012) pmid: 22810696
63. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
64. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
65. Rosell R, et al. Lancet Oncol. (2012) pmid: 22285168
66. Douillard JY, et al. Br. J. Cancer (2014) pmid: 24263064
67. Hayashi T, et al. Hum Pathol (2020) pmid: 32673682
68. Cao L, et al. Onco Targets Ther (2018) pmid: 29780256
69. Yang TY, et al. J. Clin. Oncol. (2011) pmid: 21422421
70. Sequist LV, et al. J. Clin. Oncol. (2013) pmid: 23816960
71. Qin BD, et al. Onco Targets Ther (2018) pmid: 30127622
72. Frega S, et al. J Thorac Oncol (2016) pmid: 27131295
73. Long X, et al. Onco Targets Ther (2020) pmid: 33116645
74. Mok TS, et al. J. Clin. Oncol. (2018) pmid: 29864379
75. Jänne PA, et al. N. Engl. J. Med. (2015) pmid: 25923549
76. Hong MH, et al. Cancer (2020) pmid: 32749686
77. Kim HS, et al. Oncotarget (2015) pmid: 26462025
78. Kim HS, et al. Clin. Cancer Res. (2015) pmid: 25424851
79. Mondal G, et al. Acta Neuropathol (2020) pmid: 32303840
80. Cavalieri S, et al. Eur. J. Cancer (2018) pmid: 29734047
81. Chi AS, et al. JCO Precis Oncol (2020) pmid: 32923886
82. Park K, et al. J Clin Oncol (2021) pmid: 34339292
83. Jatkoe T, et al. J Mol Diagn (2022) pmid: 35963523
84. Petrini I, et al. Onco Targets Ther (2022) pmid: 36246734
85. Goldman et al., 2022; ENA Abstract 228
86. Goldman et al., 2022; ASCO Abstract 9013
87. Jänne PA, et al. Cancer Discov (2021) pmid: 34548309
88. Ahn MJ, et al. Lancet Respir Med (2017) pmid: 29056570
89. Yang Z, et al. Sci Transl Med (2016) pmid: 27928026
90. Ahn MJ, et al. Lancet Oncol (2019) pmid: 31587882
91. Lin L, et al. Lung Cancer (2022) pmid: 35248866
92. Lu S, et al. J Clin Oncol (2022) pmid: 35580297
93. Chen JY, et al. Cancer Biol Med (2015) pmid: 26175928
94. Schoenfeld AJ, et al. Clin. Cancer Res. (2020) pmid: 31911548
95. Reck M, et al. Lancet Respir Med (2019) pmid: 30922878
96. Socinski MA, et al. J Thorac Oncol (2021) pmid: 34311108
97. Socinski MA, et al. N. Engl. J. Med. (2018) pmid: 29863955
98. Lu S, et al. Lancet Oncol (2022) pmid: 35908558
99. Vallee A, et al. Int. J. Oncol. (2013) pmid: 23934203
100. Nature (2014) pmid: 25079552
101. Nature (2012) pmid: 22960745
102. Watzka SB, et al. Eur J Cardiothorac Surg (2010) pmid: 20353893
103. Liang Z, et al. BMC Cancer (2010) pmid: 20637128
104. Grob TJ, et al. Lung Cancer (2013) pmid: 23238037
105. Park S, et al. Histol. Histopathol. (2012) pmid: 22207554
106. Dobashi Y, et al. Hum. Pathol. (2011) pmid: 21040950
107. Ludovini V, et al. Cancer Chemother. Pharmacol. (2013) pmid: 23314677
108. Skrzypski M, et al. Clin Lung Cancer (2013) pmid: 23870818
109. Kim SH, et al. Histol. Histopathol. (2012) pmid: 22419022
110. Lee JS, et al. Ann. Surg. Oncol. (2013) pmid: 23525704
111. Oakley GJ, et al. J Thorac Oncol (2011) pmid: 21587084
112. Marks JL, et al. J Thorac Oncol (2008) pmid: 18303429
113. Izar B, et al. Ann. Thorac. Surg. (2013) pmid: 23932319
114. Ciardiello F, et al. N. Engl. J. Med. (2008) pmid: 18337605
115. Lynch TJ, et al. N. Engl. J. Med. (2004) pmid: 15118073
116. Paez JG, et al. Science (2004) pmid: 15118125
117. Pao W, et al. Proc. Natl. Acad. Sci. U.S.A. (2004) pmid: 15329413
118. Yang JC, et al. Lancet Oncol. (2015) pmid: 25589191
119. Zhan T, et al. Oncogene (2017) pmid: 27617575
120. Jung YS, et al. Exp Mol Med (2020) pmid: 32037398
121. Krishnamurthy N, et al. Cancer Treat Rev (2018) pmid: 29169144
122. Kawazoe et al., 2021; ESMO Abstract 473P
123. Yamada K, et al. Cancer Res (2021) pmid: 33408116
124. Kanda Y, et al. Biochem Biophys Res Commun (2022) pmid: 34837838
125. Sanz-Ortega J, et al. Pathol. Res. Pract. (1999) pmid: 10549031
126. Poursoltan P, et al. Lung Cancer (2012) pmid: 22542170
127. Zhang Y, et al. Cancer Lett. (2011) pmid: 21255913
128. Virmani AK, et al. Clin. Cancer Res. (2001) pmid: 11448917
129. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
130. J. Natl. Cancer Inst. (2014) pmid: 24309006
131. Lu Y, et al. PLoS Med. (2006) pmid: 17194181
132. Luke JJ, et al. Clin Cancer Res (2019) pmid: 30635339
133. Logan CY, et al. Annu. Rev. Cell Dev. Biol. (2004) pmid: 15473860
134. Eklof Spink K, et al. EMBO J. (2001) pmid: 11707392
135. Liu J, et al. J. Mol. Biol. (2006) pmid: 16753179
136. Dikovskaya D, et al. J. Cell. Sci. (2010) pmid: 20144988
137. Murphy SJ, et al. Dig. Dis. Sci. (2007) pmid: 17410430
138. Aretz S, et al. Hum. Mutat. (2004) pmid: 15459959
139. Kerr SE, et al. J Mol Diagn (2013) pmid: 23159591
140. Annu Rev Pathol (2011) pmid: 21090969
141. Kastritis E, et al. Int. J. Cancer (2009) pmid: 18844223
142. Half E, et al. Orphanet J Rare Dis (2009) pmid: 19822006
143. Fritsch C, et al. Mol. Cancer Ther. (2014) pmid: 24608574
144. Juric D, et al. J. Clin. Oncol. (2018) pmid: 29401002
145. Gallant JN, et al. NPJ Precis Oncol (2019) pmid: 30793038
146. Delestre F, et al. Sci Transl Med (2021) pmid: 34613809
147. Morschhauser F, et al. Mol Cancer Ther (2020) pmid: 31619463
148. Patnaik A, et al. Ann. Oncol. (2016) pmid: 27672108
149. Santin AD, et al. Gynecol Oncol Rep (2020) pmid: 31934607
150. Damodaran S, et al. J Clin Oncol (2022) pmid: 35133871
151. André F, et al. N. Engl. J. Med. (2019) pmid: 31091374
152. Smyth LM, et al. NPJ Breast Cancer (2021) pmid: 33863913

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153. Varnier R, et al. Eur J Cancer (2019) pmid: 31351267
154. Basse C, et al. JCO Precis Oncol (2018) pmid: 32914004
155. Sultova E, et al. Arch Gynecol Obstet (2021) pmid: 33277683
156. Mackay HJ, et al. Cancer (2014) pmid: 24166148
157. Myers AP, et al. Gynecol. Oncol. (2016) pmid: 27016228
158. Dhami J, et al. Cold Spring Harb Mol Case Stud (2018) pmid: 29588307
159. Harris EJ, et al. Front Oncol (2019) pmid: 30863722
160. Hanna GJ, et al. Clin Cancer Res (2018) pmid: 29301825
161. Vansteenkiste JF, et al. J Thorac Oncol (2015) pmid: 26098748
162. Campbell JD, et al. Nat. Genet. (2016) pmid: 27158780
163. Zhao Q, et al. Future Oncol (2014) pmid: 24328409
164. Eng J, et al. J Thorac Oncol (2015) pmid: 26334752
165. Song Z, et al. Cancer Med (2016) pmid: 27554588
166. Zhang L, et al. Onco Targets Ther (2013) pmid: 23674897
167. McGowan M, et al. Lung Cancer (2017) pmid: 28024696
168. Wang Y, et al. Asian Pac. J. Cancer Prev. (2015) pmid: 26107237
169. Samuels Y, et al. Cancer Cell (2005) pmid: 15950905
170. Nat. Rev. Cancer (2009) pmid: 19629070
171. Kang S, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15647370
172. Ikenoue T, et al. Cancer Res. (2005) pmid: 15930273
173. Gymnopoulos M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17376864
174. Horn S, et al. Oncogene (2008) pmid: 18317450
175. Rudd ML, et al. Clin. Cancer Res. (2011) pmid: 21266528
176. Hon WC, et al. Oncogene (2012) pmid: 22120714
177. Burke JE, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22949682
178. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915146
179. Laurenti R, et al. Rev Saude Publica (1990) pmid: 2103068
180. Dan S, et al. Cancer Res. (2010) pmid: 20530683
181. Oda K, et al. Cancer Res. (2008) pmid: 18829572
182. Zhao L, et al. Oncogene (2008) pmid: 18794883
183. Lui VW, et al. Cancer Discov (2013) pmid: 23619167
184. Ross RL, et al. Oncogene (2013) pmid: 22430209
185. Rivière JB, et al. Nat. Genet. (2012) pmid: 22729224
186. Shibata T, et al. Cancer Lett. (2009) pmid: 19394761
187. Dogruluk T, et al. Cancer Res. (2015) pmid: 26627007
188. Croessmann S, et al. Clin. Cancer Res. (2018) pmid: 29284706
189. Ng PK, et al. Cancer Cell (2018) pmid: 29533785
190. Spangle JM, et al. (2020) pmid: 32929011
191. Chen L, et al. Nat Commun (2018) pmid: 29636477
192. Jin N, et al. J Clin Invest (2021) pmid: 34779417
193. Courtney KD, et al. J. Clin. Oncol. (2010) pmid: 20085938
194. Simpson L, et al. Exp. Cell Res. (2001) pmid: 11237521
195. Milella M, et al. Sci Rep (2017) pmid: 28220839
196. Templeton AJ, et al. Eur. Urol. (2013) pmid: 23582881
197. Sweeney C, et al. Lancet (2021) pmid: 34246347
198. de Bono JS, et al. Clin. Cancer Res. (2019) pmid: 30037818
199. Saura C, et al. Cancer Discov (2017) pmid: 27872130
200. Voss MH, et al. Clin. Cancer Res. (2018) pmid: 30327302
201. André F, et al. J. Clin. Oncol. (2016) pmid: 27091708
202. Schmid P, et al. J. Clin. Oncol. (2019) pmid: 31841354
203. Weldon Gilcrease G, et al. Invest New Drugs (2019) pmid: 30302599
204. Mendes-Pereira AM, et al. EMBO Mol Med (2009) pmid: 20049735
205. Shen Y, et al. Clin. Cancer Res. (2013) pmid: 23881923
206. Chatterjee P, et al. PLoS ONE (2013) pmid: 23565244
207. McCormick A, et al. Int. J. Gynecol. Cancer (2016) pmid: 26905328
208. Forster MD, et al. Nat Rev Clin Oncol (2011) pmid: 21468130
209. Eikesdal HP, et al. Ann Oncol (2021) pmid: 33242536
210. Dougherty et al., 2014; ASCO Abstract 5536
211. Pan M, et al. Perm J (2021) pmid: 33970096
212. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
213. Romero I, et al. Gynecol Oncol (2020) pmid: 32988624
214. Jin G, et al. Lung Cancer (2010) pmid: 20018398
215. O'Byrne KJ, et al. Lancet Oncol. (2011) pmid: 21782507
216. Spoerke JM, et al. Clin. Cancer Res. (2012) pmid: 23136191
217. Yanagawa N, et al. J Thorac Oncol (2012) pmid: 22982652
218. Cumberbatch M, et al. Clin. Cancer Res. (2014) pmid: 24284056
219. Campbell RB, et al. J. Biol. Chem. (2003) pmid: 12857747
220. Rodríguez-Escudero I, et al. Hum. Mol. Genet. (2011) pmid: 21828076
221. He X, et al. Cancer Res. (2013) pmid: 23475934
222. Han SY, et al. Cancer Res. (2000) pmid: 10866302
223. Myers MP, et al. Proc. Natl. Acad. Sci. U.S.A. (1998) pmid: 9811831
224. Pradella LM, et al. BMC Cancer (2014) pmid: 24498881
225. Kim JS, et al. Mol. Cell. Biol. (2011) pmid: 21536651
226. Denning G, et al. Oncogene (2007) pmid: 17213812
227. Hlobilkova A, et al. Anticancer Res. () pmid: 16619501
228. Redfern RE, et al. Protein Sci. (2010) pmid: 20718038
229. Shenoy S, et al. PLoS ONE (2012) pmid: 22505997
230. Wang Y, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19329485
231. Okumura K, et al. J. Biol. Chem. (2006) pmid: 16829519
232. Lee JO, et al. Cell (1999) pmid: 10555148
233. Maxwell GL, et al. Cancer Res. (1998) pmid: 9635567
234. Risinger JI, et al. Clin. Cancer Res. (1998) pmid: 9865913
235. Kato H, et al. Clin. Cancer Res. (2000) pmid: 11051241
236. Fenton TR, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22891331
237. Ngeow J, et al. J. Clin. Endocrinol. Metab. (2012) pmid: 23066114
238. Lobo GP, et al. Hum. Mol. Genet. (2009) pmid: 19457929
239. Liu J, et al. Oncogene (2014) pmid: 23995781
240. Maehama T, et al. Annu. Rev. Biochem. (2001) pmid: 11395408
241. De Vivo I, et al. J. Med. Genet. (2000) pmid: 10807691
242. Ramaswamy S, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10051603
243. Liu JL, et al. Mol. Cell. Biol. (2005) pmid: 15988030
244. Karoui M, et al. Br. J. Cancer (2004) pmid: 15026806
245. Gil A, et al. PLoS ONE (2015) pmid: 25875300
246. Furnari FB, et al. Cancer Res. (1998) pmid: 9823298
247. Spinelli L, et al. J. Med. Genet. (2015) pmid: 25527629
248. Mingo J, et al. Eur. J. Hum. Genet. (2018) pmid: 29706633
249. Wang Q, et al. J. Mol. Graph. Model. (2010) pmid: 20538496
250. Andrés-Pons A, et al. Cancer Res. (2007) pmid: 17942903
251. Butler MG, et al. J. Med. Genet. (2005) pmid: 15805158
252. Georgescu MM, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10468583
253. Staal FJ, et al. Br. J. Cancer (2002) pmid: 12085208
254. Nguyen HN, et al. Oncogene (2014) pmid: 24292679
255. Rahdar M, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19114656
256. Das S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12808147
257. Wang X, et al. Biochem. J. (2008) pmid: 18498243
258. Valiente M, et al. J. Biol. Chem. (2005) pmid: 15951562
259. Nguyen HN, et al. Oncogene (2015) pmid: 25263454
260. Shan L, et al. Cell Discov (2020) pmid: 32704382
261. Blumenthal GM, et al. Eur. J. Hum. Genet. (2008) pmid: 18781191
262. Orloff MS, et al. Oncogene (2008) pmid: 18794875
263. Zbuk KM, et al. Nat. Rev. Cancer (2007) pmid: 17167516
264. Owonikoko et al., 2016; ESMO Abstract 14230
265. Hook KE, et al. Mol. Cancer Ther. (2012) pmid: 22222631
266. Gong X, et al. Cancer Discov (2019) pmid: 30373917
267. Oser MG, et al. Cancer Discov (2019) pmid: 30373918
268. Yang W, et al. Kaohsiung J Med Sci (2022) pmid: 34741392
269. Beltran H, et al. Clin. Cancer Res. (2019) pmid: 30232224
270. Allaman-Pillet N, et al. Ophthalmic Genet. () pmid: 21955141
271. Viatour P, et al. J. Exp. Med. (2011) pmid: 21875955
272. Zhao W, et al. J Oncol (2012) pmid: 22619677
273. Burkhart DL, et al. Nat. Rev. Cancer (2008) pmid: 18650841
274. Knudsen ES, et al. Nat. Rev. Cancer (2008) pmid: 19143056
275. Berge EO, et al. Mol. Cancer (2010) pmid: 20594292
276. Giacinti C, et al. Oncogene (2006) pmid: 16936740
277. Otterson GA, et al. Proc. Natl. Acad. Sci. U.S.A. (1997) pmid: 9342358
278. Otterson GA, et al. Am. J. Hum. Genet. (1999) pmid: 10486322
279. Qin XQ, et al. Genes Dev. (1992) pmid: 1534305
280. Rubin SM, et al. Cell (2005) pmid: 16360038
281. Sun H, et al. Mol. Cell. Biol. (2006) pmid: 16449662
282. Chen Z, et al. Hum. Mutat. (2014) pmid: 24282159
283. Yun J, et al. Int J Ophthalmol (2011) pmid: 22553621
284. Houston SK, et al. Int Ophthalmol Clin (2011) pmid: 21139478
285. Ng AK, et al. Semin Radiat Oncol (2010) pmid: 19959033
286. Wu YL, et al. Lancet Oncol. (2014) pmid: 24439929
287. Passaro et al., 2019; ELCC Abstract 1150
288. Audet et al., 2013; ASCO Abstract 6041
289. Park K, et al. Lancet Oncol (2016) pmid: 27083334
290. Paz-Ares L, et al. Ann. Oncol. (2017) pmid: 28426106
291. Popat et al., 2018; IASLC WCLC Abstract P1.13-17
292. Suzuki et al., 2018; IASLC WCLC Abstract P1.01-92
293. Lau SC, et al. Clin Lung Cancer (2019) pmid: 31178389
294. Thongprasert S, et al. Lung Cancer Manag (2019) pmid: 31807143
295. Chang et al., 2018; IASLC WCLC Abstract P1.01-11
296. Llinás-Quintero N, et al. Case Rep Oncol Med (2019) pmid: 31637072
297. Miller VA, et al. Lancet Oncol. (2012) pmid: 22452896
298. Chen X, et al. Lung Cancer (2013) pmid: 23664448
299. Katakami N, et al. J. Clin. Oncol. (2013) pmid: 23816963
300. Landi L, et al. Clin Lung Cancer (2014) pmid: 25242668
301. De Grève J, et al. Lung Cancer (2015) pmid: 25682316
302. Yang JC, et al. Lancet Oncol. (2015) pmid: 26051236
303. Horn L, et al. Lung Cancer (2017) pmid: 29110849
304. Yamamoto N, et al. Adv Ther (2020) pmid: 31863283

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305. Soria JC, et al. Lancet Oncol. (2015) pmid: 26156651
306. Schuler M, et al. Ann. Oncol. (2016) pmid: 26646759
307. Wu YL, et al. Lancet Oncol. (2017) pmid: 28958502
308. Opsomer RJ, et al. Acta Urol Belg (1985) pmid: 2986437
309. Wu et al., 2018; WCLC abstract MA26.11
310. Ramalingam SS, et al. Ann. Oncol. (2016) pmid: 26768165
311. Li HS, et al. J Thorac Dis (2022) pmid: 35693621
312. van Geel RMJM, et al. Br. J. Cancer (2020) pmid: 32147669
313. Reckamp KL, et al. Cancer (2014) pmid: 24501009
314. Park K, et al. J Thorac Oncol (2014) pmid: 25521398
315. Cappuzzo F, et al. Lancet Oncol. (2010) pmid: 20493771
316. Zhong WZ, et al. J. Clin. Oncol. (2019) pmid: 31194613
317. Petrelli F, et al. Clin Lung Cancer (2012) pmid: 22056888
318. Leon et al., 2014; doi.org/10.1093/annonc/mdu349.52
319. Lee CK, et al. J. Natl. Cancer Inst. (2017) pmid: 28376144
320. Yang JJ, et al. Br. J. Cancer (2017) pmid: 28103612
321. Zhou Q, et al. Cancer Cell (2021) pmid: 34388377
322. Kawashima Y, et al. Lancet Respir Med (2022) pmid: 34454653
323. Saito H, et al. Lancet Oncol (2019) pmid: 30975627
324. Piccirillo et al., 2021; ESMO Abstract 12070
325. Faehling M, et al. J Cancer Res Clin Oncol (2018) pmid: 29687154
326. Nakagawa K, et al. Lancet Oncol. (2019) pmid: 31591063
327. Han JY, et al. J. Clin. Oncol. (2012) pmid: 22370314
328. Maemondo M, et al. N. Engl. J. Med. (2010) pmid: 20573926
329. Mitsudomi T, et al. Lancet Oncol. (2010) pmid: 20022809
330. Mok TS, et al. N. Engl. J. Med. (2009) pmid: 19692680
331. Qi WX, et al. Curr Med Res Opin (2015) pmid: 25329826
332. Zhao H, et al. J Thorac Oncol (2015) pmid: 25546556
333. Wang J, et al. Int. J. Cancer (2019) pmid: 30255937
334. Baik CS, et al. J Thorac Oncol (2015) pmid: 26398831
335. Yoshioka H, et al. Ann. Oncol. (2019) pmid: 31553438
336. Fukuoka M, et al. J. Clin. Oncol. (2011) pmid: 21670455
337. Sutiman N, et al. J Thorac Oncol (2017) pmid: 27908825
338. Noronha V, et al. J. Clin. Oncol. (2019) pmid: 31411950
339. Hosomi Y, et al. J. Clin. Oncol. (2020) pmid: 31682542
340. Creelan BC, et al. Br J Cancer (2021) pmid: 33012782
341. Soria JC, et al. N. Engl. J. Med. (2018) pmid: 29151359
342. Alanazi A, et al. Lung Cancer Manag (2020) pmid: 33318755
343. Kim et al., 2021; DOI: 10.1200/PO.20.00296
344. Ramalingam SS, et al. N. Engl. J. Med. (2019) pmid: 31751012
345. Tsuboi et al., 2022; ESMO Abstract LBA47
346. Kenmotsu H, et al. J Thorac Oncol (2022) pmid: 35636696
347. Soo et al., 2021; ESMO Abstract VP3-2021
348. Oxnard GR, et al. Ann. Oncol. (2020) pmid: 32139298

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