FOUNDATIONONE®LIQUID CDx

PATIENT

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

REPORT DATE

COUNTRY CODE
TR

ORDERED TEST #

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

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

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings

Blood Tumor Mutational Burden - 1 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

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

EGFR T790M, exon 19 deletion (E746_A750del)
DNMT3A C497fs*154, R882C
EPHB1 A922T
NOTCH2 L1862*
RAD21 R554fs*57
TET2 Q705*
TP53 S241F

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Osimertinib** (p. 11)
- Targeted therapies with **potential resistance** based on this patient's genomic findings: **Afatinib** (p. 12), **Dacomitinib** (p. 13), **Erlotinib** (p. 14), **Gefitinib** (p. 14)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 16)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A*** **C497fs*154, R882C** (p. 7), ***TET2*** **Q705*** (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 1 Muts/Mb	**No therapies or clinical trials. See Biomarker Findings section**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
Tumor Fraction - Elevated Tumor Fraction Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).**

GENOMIC FINDINGS		VAF %
EGFR -	T790M	0.26%
	exon 19 deletion (E746_A750del)	1.4%

10 Trials see p. 16

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	
Osimertinib	1
Afatinib	⊗
Dacomitinib	⊗
Erlotinib	⊗
Gefitinib	⊗

THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
None

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *NCCN category*

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

DNMT3A - C497fs*154, R882C ..... p. 7

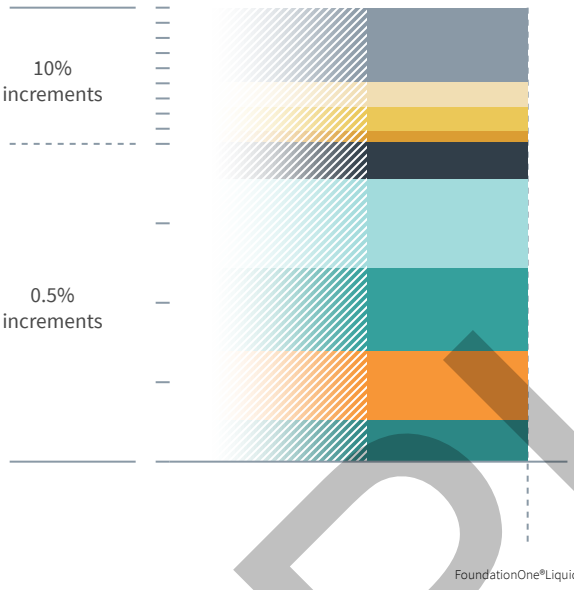
TET2 - Q705* ..... p. 9

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies 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/or exhaustive. Neither the therapies 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 or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC*, *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF1*, *NF2*, *PALB2*, *PMS2*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.



HISTORIC PATIENT FINDINGS		VAF%
Blood Tumor Mutational Burden		1 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
EGFR	exon 19 deletion (E746_A750del)	1.4%
	T790M	0.26%
DNMT3A	C497fs*154	16.1%
	R882C	0.56%
EPHB1	A922T	48.6%
NOTCH2	L1862*	0.44%
RAD21	R554fs*57	16.2%
TET2	Q705*	7.4%
TP53	S241F	0.52%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the

complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

BIOMARKER

Blood Tumor Mutational Burden

RESULT
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)[3]. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic non-small cell lung cancer (NSCLC) reported that bTMB ≥7 Muts/Mb was associated with shorter PFS (2.8 vs. 4.2 months) and OS (7.4 vs. 11.9 months) compared with bTMB <7 Muts/Mb for patients treated with docetaxel[5]. In one study of advanced NSCLC in China, bTMB ≥6 Muts/Mb was associated with decreased PFS (10 vs. 18 months) and OS (11 vs. 25 months) compared with bTMB <6 Muts/Mb for patients treated with platinum-based chemotherapy[6]. 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[7]. 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)[8]. 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[9]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[9-10].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[11-12] and cigarette smoke in lung cancer[13-14], treatment with temozolomide-based chemotherapy in glioma[15-16], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[17-21], and microsatellite instability (MSI)[17,20-21]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample 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[1-3]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[22-27].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[28]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[29], Ewing sarcoma and osteosarcoma[30], prostate cancer[25], breast cancer[31], leiomyosarcoma[32], esophageal cancer[33], colorectal cancer[34], and gastrointestinal cancer[35].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[36], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[37-38].

GENE
EGFR

ALTERATION
T790M, exon 19 deletion (E746_A750del)

TRANSCRIPT ID
NM_005228, NM_005228

CODING SEQUENCE EFFECT
2369C>T, 2235_2249delGGAATTAAGAGAAGC

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[39], gefitinib[40], afatinib[41], dacomitinib[42], and osimertinib[43]; however, the data for patients with other tumor types are limited[44-49]. The efficacy of third-generation EGFR inhibitors that selectively target EGFR T790M in non-small cell lung cancer (NSCLC) has been confirmed in osimertinib[43,50-53], D-0316[54], abivertinib[55-56], alflutinib[57], naquotinib[58-61], nazartinib[62], and olmutinib[63-64]. The Phase 1 CHRYSALIS study of amivantamab monotherapy or 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[65-68] . 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[69]. 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[70-71]. 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[72]. 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[73]. OR was observed in a numerically higher proportion of patients with the EGFR T790M mutation than those without this mutation[73]. The presence of a TP53 mutation, as seen here, independently associated with significantly shorter median PFS (9 vs. 14 months) and OS (16 vs. 24 months) for patients with T790M-positive metastatic NSCLC treated with second-line osimertinib[74].

— Potential Resistance —

The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, confers clinical resistance to gefitinib[75-78], erlotinib[75-76,78], afatinib[79-82], and dacomitinib[78,83-85]. Preclinical resistance to lapatinib has also been reported[86-87].

— Nontargeted Approaches —

Patients with EGFR-mutated non-squamous metastatic non-small cell lung cancer previously treated with EGFR TKI have benefited from immune checkpoint inhibitors combined with anti-angiogenic and chemotherapy, particularly atezolizumab plus bevacizumab plus carboplatin and paclitaxel (OS HR 0.61 compared with bevacizumab/chemotherapy)[88-90] or sintilimab plus bevacizumab biosimilar plus cisplatin and pemetrexed (PFS HR 0.46 compared with chemotherapy alone)[91].

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[92-94] and in 4% of lung squamous cell carcinomas[95]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[96-101]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[102-103]. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[104-105]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[106] or resected Stage 1 NSCLC[107]. In a retrospective study of lung adenocarcinoma treated with surgical resection without neoadjuvant TKIs, significantly shorter OS and recurrence-free survival was observed for patients harboring uncommon EGFR mutations (G719X, T790M, or L861R/Q) compared with those harboring only common mutations (L858R or exon 19 deletion)[108].

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[109]. EGFR exon 19 deletion mutations, such as seen here, have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib[110-112], afatinib[113], osimertinib[53], and dacomitinib[42,114], although limited preclinical data suggest reduced sensitivity to lapatinib[87,115]. The EGFR T790M mutation, when co-occurring with EGFR activating alterations, has been associated with clinical resistance to gefitinib[75-78], erlotinib[75-76,78], dacomitinib[78,83-85], and afatinib[79-82,116], as well as preclinical resistance to lapatinib[86-87]. Rare cases of EGFR T790M without a concurrent activating alteration have been reported[117] and germline T790M mutations have been reported to predispose to familial lung adenocarcinoma[117-119]. Limited preclinical data suggests T790M alone is weakly activating, and increased EGFR activity is observed when T790M is expressed with certain activating EGFR alterations[120]. Therefore, although this alteration has not been fully characterized, it is likely to result in reduced sensitivity to first- and second-generation EGFR inhibitors.

GENE
DNMT3A

ALTERATION
C497fs*154, R882C

TRANSCRIPT ID
NM_022552, NM_022552

CODING SEQUENCE EFFECT
1488delC, 2644C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2022)[121-122]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2022).

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[123-124]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[125-130]. Mutations at codon 882, including R882S, R882H, and R882C, have demonstrated reduced methyltransferase activity in vitro, with R882H and R882C conferring increased cell proliferation[131-133]. About half of all DNMT3A mutations in AML are R882H, which leads to a partially defective enzyme and altered oligomerization behavior, although the effect on global methylation remains to some extent controversial; in addition, at least one report suggests that mutation of R882 is associated with sensitivity to DNA methyltransferase inhibitors[131-134]. On the basis of this, any alteration at R882 is likely to promote tumorigenesis, although the efficacy of DNMT inhibitors may not be consistent for all mutations. Alterations such as seen here may disrupt DNMT3A function or expression[135-138].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[139-144]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[139-140]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[145]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[143,146-147]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
EPHB1

ALTERATION
A922T

TRANSCRIPT ID
NM_004441

CODING SEQUENCE EFFECT
2764G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The tyrosine kinase inhibitors dasatinib, nilotinib, and bosutinib have shown in vitro activity against EPHB1[148-150]; however, further investigations are warranted to determine if these therapeutic approaches would be relevant for tumors with EPHB1 alterations. There are no approved therapies that directly address EPHB1 alterations, although a variety of therapeutic approaches targeting Eph receptors and ligands are under preclinical and clinical development[150-151].

FREQUENCY & PROGNOSIS

In the TCGA datasets, EPHB1 mutations have been reported with highest incidences in lung squamous cell carcinomas (10%)[95], uterine corpus endometrioid carcinomas (7%)[17], lung adenocarcinomas (7%)[94], and stomach adenocarcinomas (7%)[152]. In one study of non-small cell lung carcinomas (NSCLC), EPHB1 mutations were found in 20% (16/81) of analyzed samples[153]. The effects of EPHB1 alterations vary by tumor type. Loss of EPHB1 has been reported in breast[154], gastric[155], colorectal[156], renal cell[157], serous ovarian[158], cervical[159], and lung cancer[160]; EPHB1 loss has been correlated with cell invasiveness, tumor progression, and metastasis. In the context of serous ovarian carcinoma, loss of EPHB1 protein is associated with high tumor grade and poor overall survival[158]. Aberrant methylation patterns leading to EPHB1 inactivation have been observed in acute lymphoblastic leukemia bone marrow samples and leukemia cell lines[161]. In contrast, upregulation or amplification of EPHB1 has been observed in other cancers, including rhabdomyosarcoma[162] and oligodendroglioma[163]. EPHB1 expression level is associated with good survival outcome in patients with malignant astrocytomas, including anaplastic astrocytoma and glioblastoma multiforme (GBM)[163], as well as gallbladder cancer[164].

FINDING SUMMARY

EPHB1 encodes a member of the Eph family of receptor tyrosine kinases[165]. Ephrin signaling has been implicated in multiple processes, including cell adhesion, cytoskeletal organization, and cell migration[166]. EphB receptors, including EPHB1, have been identified to undergo dysregulation (amplification, mutation, under- or overexpression) in a number of different cancer types[167].

GENE
NOTCH2

ALTERATION
L1862*

TRANSCRIPT ID
NM_024408

CODING SEQUENCE EFFECT
5585T>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Several approaches for inhibiting NOTCH2 signaling have been developed, including neutralizing NOTCH antibodies such as tarextumab (OMP-59R5)[168], which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSI). In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PR in 15% (6/39) and SD in 54% (21/39) of patients with metastatic adenoid cystic carcinoma harboring NOTCH activating alterations[169]. A study of several cohorts of patients with NSCLC reported an association between deleterious NOTCH mutations (NOTCH1-3 considered as a pooled set) and improved clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors[170]. However, as presence of NOTCH mutation correlates with higher TMB, the independent predictive power of NOTCH alterations is not entirely clear; furthermore, significant associations with improved clinical benefit were not found for mutations in NOTCH1, NOTCH2, or NOTCH3 considered individually, and the study did not delineate clinical associations for different types of NOTCH alterations[170]. Therefore, it is unclear if the alteration seen here would predict efficacy of treatment with an immune checkpoint inhibitor. These approaches would not be relevant in the context of inactivating alterations, as seen here.

FREQUENCY & PROGNOSIS

NOTCH2 mutations have been reported in 1-9% of lung adenocarcinomas[14,93-94,171] and 7% of lung squamous cell carcinomas[95]. Upregulation of NOTCH2 has been found to be associated with progression of early-stage lung adenocarcinoma, and with aggressiveness as the disease progresses[172].

FINDING SUMMARY

NOTCH2 encodes a member of the NOTCH family of receptors, which play a role in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves gamma-secretase (GS) cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[173-174]. Depending on cellular context, NOTCH2 can act as either a tumor suppressor or an oncogene[175-179]. NOTCH2 alterations that disrupt or remove the RAM domain (amino acids 1699-1826), ANK repeat region (amino acids 1827-2040), and/or TAD (amino acids 2039-2287), which are necessary for the transcriptional activity of NOTCH family proteins, are predicted to be inactivating[180-181].

GENE
RAD21

ALTERATION
R554fs*57

TRANSCRIPT ID
NM_006265

CODING SEQUENCE EFFECT
1660_1663delAGAA

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to target alterations in this gene.

FREQUENCY & PROGNOSIS

RAD21 amplifications have been reported in solid tumors, including breast cancers (7%), melanoma (5.4%), and prostate (2.4%) cancers[182]. RAD21 overexpression has been correlated with poor prognosis in endometrial cancer[183], breast cancer[184-185], Ewing sarcoma[186], and colorectal cancer (CRC), especially in KRAS-mutant CRC[187].

FINDING SUMMARY

RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[188-191]. In preclinical studies, downregulation of RAD21 or other cohesin components leads to loss of expression from amplified genes, as well as amplifications themselves upon cell passaging[192], but also leads to an increase in deletions, insertions, and other rearrangements[193]. High RAD21 expression has also been associated with increased genomic instability[194]. Cohesin complex also organizes chromatin domains and regulates gene expression[195-196]. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression[197]. RAD21 amplification has been correlated with increased expression in breast[184,194,198] and endometrial[183] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

GENE
TET2

ALTERATION
Q705*

TRANSCRIPT ID
NM_001127208

CODING SEQUENCE EFFECT
2113C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2022)[121-122]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2022).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[199-200]. Alterations such as seen here may disrupt TET2 function or expression[201-205].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[139-144]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[139-140]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[145]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[143,146-147]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
TP53

ALTERATION
S241F

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
722C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[206-209], or p53 gene therapy and immunotherapeutics such as SGT-53[210-214] and ALT-801[215]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[216]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[217]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[218]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[219]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[220]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[221]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[222]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[214]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[223-225]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[226]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[227-228]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[229-230]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition. The presence of a TP53 mutation, as seen here, independently associated with significantly shorter median PFS (9 vs. 14 months) and OS (16 vs. 24 months) for patients with T790M-positive metastatic NSCLC treated with second-line osimertinib[74].

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[94-95,231-236], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2022)[93-95,237]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2022)[121-122]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[238]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[239].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[240]. Alterations such as seen here may disrupt TP53 function or expression[241-245].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Mar 2022)[246]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[247-249], including sarcomas[250-251]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[252] to 1:20,000[251]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[253]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[139-144]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[139-140]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[145]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[143,146-147]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Osimertinib

Assay findings association

EGFR
T790M, exon 19 deletion (E746_A750del)

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[43,53,254-256] . 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[53].

SUPPORTING DATA

The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months; HR=0.80) for patients with advanced NSCLC and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858)[53,257] . In the Phase 3 ADAURA study, patients with early Stage (IB/II/IIIA) EGFR-mutated NSCLC experienced longer PFSs on osimertinib compared to placebo in the adjuvant setting (not reached vs. 28.1 months; HR=0.21)[258]. 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[43]. 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% (4/19), a DCR of 81%, and mPFS of 11 months (Kim et al., 2021 AACR Abstract CT163). In a Phase 3 study for patients with EGFR T790M-positive advanced NSCLC who progressed on EGFR TKI therapy, osimertinib compared with combination platinum therapy led to longer median PFS (10.1 months vs. 4.4 months), including for patients with central nervous system metastases (8.5 vs. 4.2 months). An ORR of 71% was achieved with osimertinib compared to 31% with combination platinum therapy[259]. The efficacy of osimertinib is confirmed by earlier phase studies in this setting[43,50-52] , and in a real-world setting for patients with T790M-positive advanced NSCLC pretreated with EGFR TKIs[260-261] . Case studies report that 2 patients with T790M-mutated NSCLC achieved durable PRs to osimertinib rechallenge after the adverse events induced by initial osimertinib treatment had been resolved[262-263] . 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)[264]. 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)[265]. 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[266].

Afatinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
T790M, exon 19 deletion (E746_A750del)

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[41-42,267-268] , whereas data for patients with other tumor types are limited[44-49,269] . EGFR T790M, in the presence of a co-occurring activating EGFR alteration, has been associated with clinical resistance to afatinib and has been reported in 33-48% of patients who progressed on the inhibitor across multiple studies[79-82,116] . Although DCRs of more than 50% have been reported for patients with erlotinib- or gefitinib-resistant NSCLC treated with afatinib[270], including T790M-positive patients[271], 1 study observed that overall survival for patients with T790M-positive NSCLC was worse than for patients who were T790M-negative (HR=1.79, p=0.005)[272].

SUPPORTING DATA

Afatinib enabled a DCR of 64.3% (9/14) for patients with advanced T790M-positive NSCLC in a post-hoc analysis of Phase 2 and Phase 3 trials[271]. For T790M-positive patients who were TKI-naive or -pretreated, afatinib treatment resulted in ORRs of 24.0% (6/25) and 18.8% (12/64), respectively, in a large-scale retrospective analysis of EGFR-mutated NSCLC[273]. Another large-scale 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 21.1% (4/19) for T790M-positive patients and an ORR of 24.4% (105/431) for the entire cohort[274]. For heavily pre-treated patients with erlotinib- or gefitinib-resistant NSCLC and T790M-positivity, the combination of afatinib with cetuximab enabled an ORR of 31.7% (40/126) in a Phase 1b study[275], and 1/1 PR in a case series[276]. A patient with T790M-positive NSCLC who progressed on erlotinib experienced a PR to afatinib combined with panitumumab in another case series[277]. Afatinib has shown significant clinical activity for patients with NSCLC and the EGFR common sensitizing mutations L858R or exon 19 deletions, based on extensive clinical evidence[41,267,278-281] . Two randomized Phase 3 trials reported significantly improved median PFS from afatinib compared with chemotherapy for patients with EGFR common sensitizing mutations (LUX-Lung 3, 13.6 vs. 6.9 months, HR 0.47, p<0.001; LUX-Lung 6, 11.0 vs. 5.6 months, HR 0.28, p<0.0001)[41,267] . However, while afatinib significantly increased OS relative to chemotherapy for patients with EGFR exon 19 alterations in these two trials (LUX-Lung 3, 33.3 vs. 21.1 months, HR=0.54; LUX-Lung 6, 31.4 vs. 18.4 months, HR=0.64), no significant OS differences were observed in treatment for patients with L858R mutation[113]. A similar alteration-specific difference was observed for EGFR-mutated treatment-naive NSCLC in a retrospective analysis, which reported numerically longer median OS from second- versus first-generation EGFR TKIs (48.8 vs. 26.4 months, HR=0.59) for patients with exon 19 deletions, but no substantial difference for patients with L858R (25.4 vs. 20.6 months, HR=0.90)[278]. A Phase 2b study of first-line afatinib compared with gefitinib, also for NSCLC with exon 19 deletions or L858R, reported similar median OS for the two therapies (27.9 vs. 24.5 months, HR=0.86) but significantly longer time-to-treatment-failure (13.7 vs. 11.5 months, HR=0.75) and higher ORR (73% vs. 56%, p=0.0018) with afatinib[279]. Patients with metastatic NSCLC and common EGFR mutations who progressed on prior chemotherapy experienced an ORR of 50.0% (30/60) from afatinib in a Phase 4 trial[280]. As first-line therapy for NSCLC with EGFR exon 19 deletions or L858R, prospective or randomized Phase 2 trials have reported a median PFS of 10.2 months and OS of 24.8 months for patients unfit for chemotherapy[281] and an ORR of 72.5% (n=40, 1 CR), DCR of 100% (40/40), and median PFS and OS of 15.2 and 30.0 months, respectively, for elderly patients ≥70 years old[282]. A retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 27.4% (63/230) for patients with common sensitizing EGFR mutations and an ORR of 24.4% (105/431) for the entire cohort[283]. 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[284]. 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%[270-271,285-288] ; however, DCRs of more than 50% have been observed[270]. 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[289] or osimertinib[290], respectively. Extensive clinical data have demonstrated that afatinib is effective for patients with EGFR-mutated advanced NSCLC, including exon 19 deletions and L858 mutations, as well as uncommon sensitizing mutations in exons 18 or 20[41,113,267,279,281,283,291] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[270,292-302] . 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 median OS (7.9 vs. 6.8 months, HR=0.81), significantly longer median PFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[291]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[303].

Dacomitinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
T790M, exon 19 deletion (E746_A750del)

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[41-42,267-268] , whereas data for patients with other tumor types are limited[44-49,269] . Patients with untreated advanced NSCLC and EGFR exon 19 deletions achieved an ORR of 76%[114] and a median OS of 34.1 months with dacomitinib[42]. EGFR T790M, in the presence of a co-occurring activating EGFR alteration, is associated with clinical resistance to dacomitinib[78,83-84,304-305] .

SUPPORTING DATA

A randomized Phase 3 trial in patients with NSCLC with activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS, 34.1 vs. 26.8 months, HR=0.760; median PFS, 14.7 vs. 9.2 months, HR=0.59)[114,306] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[307]. A pooled subgroup analysis of patients with NSCLC with activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (median PFS, 14.6 vs, 9.6 months, HR=0.717; median OS, 26.6 vs, 23.2 months, HR=0.737)[308]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[78,83-84] . 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[309]. A Phase 2 study of dacomitinib in patients with NSCLC who had been previously treated with chemotherapy or erlotinib and were not selected for EGFR mutations reported an ORR of 4.5% (3/66)[78]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[310].

Erlotinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
T790M, exon 19 deletion (E746_A750del)

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[39,311-313] . The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, has been associated with resistance to erlotinib and gefitinib[75-78] .

SUPPORTING DATA

In one study, median PFS (4.1 vs. 11.7 months, HR=9.7) and median OS (14.1 vs. 47.0 months, HR=10.2) were significantly shorter for patients with non-small cell lung cancer (NSCLC) harboring EGFR L747_A750>P (n=6) relative to those with deletions affecting EGFR E746_A750 (n=24) treated with first-line erlotinib[314]. 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)[39,315] . This study and meta-analyses attribute the lack of OS benefit to the effectiveness of post-progression salvage therapy in the control arm[316]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[317]. 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)[318], the NEJ026 trial for Japanese patients (16.9 vs. 13.3 months, HR=0.605)[319-320] , and the international BEVERLY trial (15.4 vs. 9.7 months, HR=0.60)[321]; 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[311,322] . 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[312]. 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)[323].

Gefitinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
T790M, exon 19 deletion (E746_A750del)

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[313,324-329] , and responses have been reported for patients with EGFR-rearranged NSCLC[256,330] . The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, has been associated with resistance to erlotinib and gefitinib[75-78] .

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[40]. Phase 3 studies for Japanese patients[326,331] and East Asian patients[327,332] 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)[333]. 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[334-335] . 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[336].

THERAPIES ASSOCIATED WITH RESISTANCE IN PATIENT'S TUMOR TYPE

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

IMPORTANT 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. There may also be compassionate use or early access programs available, which are not listed in this report. 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 are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. 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. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
EGFR

ALTERATION
T790M, exon 19 deletion (E746_A750del)

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. In the context of co-occurring activating alterations, EGFR T790M confers clinical resistance to erlotinib, gefitinib, afatinib, lapatinib, and dacomitinib. Other agents may be relevant, including irreversible EGFR inhibitors, and in the context of lung cancer, the ALK/EGFR/ROS1 inhibitor brigatinib.

NCT04487080

PHASE 3

A Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib in Locally Advanced or Metastatic Non-Small Cell Lung Cancer

TARGETS
MET, EGFR

LOCATIONS: Istanbul (Turkey), Edirne (Turkey), Izmir (Turkey), Konya (Turkey), Adana (Turkey), Haifa (Israel), Gyöngyös (Hungary), Torokbalint (Hungary), Budapest (Hungary), Szekesfehervar (Hungary)

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: Ramat Gan (Israel), Haifa (Israel), Marseille CEDEX 05 (France), Dijon (France), Toulouse (France), Barcelona (Spain), Bordeaux (France), Madrid (Spain), Majadahonda (Spain), Malaga (Spain)

NCT02824952

PHASE 2

Neo-adjuvant Trial With AZD9291 in EGFRm+ Stage IIIA/B NSCLC

TARGETS
EGFR

LOCATIONS: Jerusalem (Israel)

NCT02609776

PHASE 1

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

TARGETS
MET, EGFR

LOCATIONS: Napoli (Italy), Ravenna (Italy), Marseille (France), Lyon Cedex 8 (France), Dijon (France), Barcelona (Spain), Villejuif Cedex (France), Paris (France), Bordeaux (France), Sutton (United Kingdom)

CLINICAL TRIALS

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: Napoli (Italy), Ravenna (Italy), Gauting (Germany), Milano (Italy), Monza (Italy), Berlin (Germany), Halle (Saale) (Germany), Stuttgart (Germany), Frankfurt am Main (Germany), Marseille (France)

NCT04233021

PHASE 2

Study of Osimertinib in Patients With a Lung Cancer With Brain or Leptomeningeal Metastases With EGFR Mutation

TARGETS
EGFR

LOCATIONS: Colmar (France), Toulon (France), Strasbourg (France), Grenoble (France), Aix-en-Provence (France), Marseille (France), Besançon (France), Avignon (France), Lyon (France), Pierre-Bénite (France)

NCT03865511

PHASE 2

MEchanisms of Resistance in EGFR Mutated Nonpretreated Advanced Lung Cancer Receiving OSimErtib

TARGETS
EGFR

LOCATIONS: Toulon (France), Le Mans (France), Cholet (France), Nantes (France)

NCT02099058

PHASE 1

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

TARGETS
MET, EGFR, PD-1

LOCATIONS: Marseille CEDEX 05 (France), Massachusetts, Seoul (Korea, Republic of), Suwon (Korea, Republic of), New York, New Jersey, Taipei City (Taiwan), Virginia, Tainan (Taiwan)

NCT03783403

PHASE 1

A Study of CC-95251, a Monoclonal Antibody Directed Against SIRPα, in Subjects With Advanced Solid and Hematologic Cancers

TARGETS
CD20, EGFR, SIRP-alpha

LOCATIONS: Creteil (France), Rouen (France), Borddeaux Cedex (France), Nantes Cedex 01 (France), New York, Seoul (Korea, Republic of), Toronto (Canada), Pennsylvania, Edmonton (Canada), North Carolina

NCT04606381

PHASE 1

A Study of Amivantamab Subcutaneous (SC) Administration for the Treatment of Advanced Solid Malignancies

TARGETS
MET, EGFR

LOCATIONS: Sutton (United Kingdom), Manchester (United Kingdom), Seoul (Korea, Republic of), New York, Toronto (Canada), Indiana, Tennessee

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.

ARID1A
P1897A

ATM
E1704K and S333F

C11ORF30 (EMSY)
V114I

CBL
V581I

DNMT3A
V328F

ERRFI1
H250L

JAK2
Y868*

SPEN
R1339C

APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B or WTX)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	***CCND1***	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*	***CD274*** **(PD-L1)**	*CDC73*
CDH1	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*	***CDKN2A***	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2 **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EMSY* (C11orf30)	*EP300*	*EPHA3*
EPHB1	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***	***ESR1*** **Exons 4-8**
*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FANCA*	*FANCC*	*FANCG*
FANCL	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*	*FLCN*	*FLT1*
FLT3 **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*	*GID4* (C17orf39)	***GNA11*** **Exons 4, 5**
GNA13	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3-3A* (H3F3A)	*HDAC1*	*HGF*	*HNF1A*
HRAS **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*	*INPP4B*
IRF2	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*	*KDM5C*
KDM6A	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)	

APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*
MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***
MITF	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*MRE11* (MRE11A)	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*
MTAP	***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*
NF1	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**
NRAS **Exons 2, 3**	*NSD2* (WHSC1 or MMSET)	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*
PALB2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**
PDGFRB **Exons 12-21, 23**	*PDK1*	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*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*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*
RET Introns 7, 8, **Exons 11, 13-16, Introns 9-11**	*RICTOR*	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*
SDHC	*SDHD*	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*
SMARCB1	***SMO***	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*
STAG2	*STAT3*	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C* (FAM46C)	*TERC** ncRNA
TERT* **Promoter**	*TET2*	*TGFBR2*	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*
TSC2	*TYRO3*	*U2AF1*	***VEGFA***	*VHL*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*
ZNF703								

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Blood Tumor Mutational Burden (bTMB)
Tumor Fraction

FoundationOne Liquid 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. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid 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.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx 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 malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

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. *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.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

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.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited

to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

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.

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 >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, 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.

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.

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 Liquid CDx.

TREATMENT DECISIONS ARE THE 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 of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, 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 6.3.0

1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
4. Li et al., 2020; ASCO Abstract 6511
5. Nie W, et al. J Natl Compr Canc Netw (2020) pmid: 32380463
6. Ma Y, et al. Front Oncol (2021) pmid: 34055609
7. Meng G, et al. PLoS One (2022) pmid: 35113949
8. Xiao D, et al. Oncotarget (2016) pmid: 27009843
9. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
10. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
11. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
12. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
13. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
14. Rizvi NA, et al. Science (2015) pmid: 25765070
15. Johnson BE, et al. Science (2014) pmid: 24336570
16. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
17. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
18. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
19. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
20. Nature (2012) pmid: 22810696
21. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
22. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
23. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
24. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
25. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
26. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
27. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
28. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
29. Lapin M, et al. J Transl Med (2018) pmid: 30400802
30. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
31. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
32. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
33. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
34. Fan G, et al. PLoS ONE (2017) pmid: 28187169
35. Vu et al., 2020; DOI: 10.1200/PO.19.00204
36. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
37. Zhang EW, et al. Cancer (2020) pmid: 32757294
38. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
39. Rosell R, et al. Lancet Oncol. (2012) pmid: 22285168
40. Douillard JY, et al. Br. J. Cancer (2014) pmid: 24263064
41. Sequist LV, et al. J. Clin. Oncol. (2013) pmid: 23816960
42. Mok TS, et al. J. Clin. Oncol. (2018) pmid: 29864379
43. Jänne PA, et al. N. Engl. J. Med. (2015) pmid: 25923549
44. Hong MH, et al. Cancer (2020) pmid: 32749686
45. Kim HS, et al. Oncotarget (2015) pmid: 26462025
46. Kim HS, et al. Clin. Cancer Res. (2015) pmid: 25424851
47. Mondal G, et al. Acta Neuropathol (2020) pmid: 32303840
48. Cavalieri S, et al. Eur. J. Cancer (2018) pmid: 29734047
49. Chi AS, et al. JCO Precis Oncol (2020) pmid: 32923886
50. Yang JCH, et al. J. Clin. Oncol. (2019) pmid: 31809241
51. Yang JC, et al. J. Clin. Oncol. (2017) pmid: 28221867
52. Goss G, et al. Lancet Oncol. (2016) pmid: 27751847
53. Soria JC, et al. N. Engl. J. Med. (2018) pmid: 29151359
54. Lu et al., 2021; AACR Abstract CT170
55. Wang H, et al. Thorac Cancer (2020) pmid: 31943845
56. Ma Y, et al. J Thorac Oncol (2018) pmid: 29626621
57. Shi Y, et al. Lancet Respir Med (2021) pmid: 33780662
58. Azuma K, et al. Cancer Sci (2018) pmid: 29807396
59. Kelly RJ, et al. Ann Oncol (2019) pmid: 31070709
60. Murakami H, et al. Cancer Sci (2018) pmid: 29972716
61. Yu HA, et al. Clin Cancer Res (2017) pmid: 28954786
62. Tan DS, et al. Lancet Respir Med (2020) pmid: 31954624
63. Park K, et al. Cancer (2021) pmid: 33434335
64. Kim DW, et al. Lung Cancer (2019) pmid: 31447004
65. Leighl et al., 2021; ESMO Abstract 1192MO
66. Cho et al., 2020; ESMO Abstract 1258O
67. Bauml et al., 2021; ASCO Abstract 9006
68. Shu et al., 2021; ESMO Abstract 1193MO
69. Jänne PA, et al. Cancer Discov (2021) pmid: 34548309
70. Ahn MJ, et al. Lancet Respir Med (2017) pmid: 29056570
71. Yang Z, et al. Sci Transl Med (2016) pmid: 27928026
72. Ahn MJ, et al. Lancet Oncol (2019) pmid: 31587882
73. Lin L, et al. Lung Cancer (2022) pmid: 35248866
74. Roeper et al., 2022; DOI: 10.21037/tlcr-21-754
75. Sequist LV, et al. Sci Transl Med (2011) pmid: 21430269
76. Pao W, et al. PLoS Med. (2005) pmid: 15737014
77. Kosaka T, et al. Clin. Cancer Res. (2006) pmid: 17020982
78. Reckamp KL, et al. Cancer (2014) pmid: 24501009
79. Wu SG, et al. Oncotarget (2016) pmid: 26862733
80. Lee K, et al. Lung Cancer (2019) pmid: 30885357
81. Lin YT, et al. Int J Cancer (2019) pmid: 30485437
82. Kaburagi T, et al. Anticancer Res (2018) pmid: 29715155
83. Jänne PA, et al. Clin. Cancer Res. (2011) pmid: 21220471
84. Yu HA, et al. Lung Cancer (2017) pmid: 29191595
85. Ercan D, et al. Oncogene (2010) pmid: 20118985
86. Avizienyte E, et al. Biochem. J. (2008) pmid: 18588508
87. Gilmer TM, et al. Cancer Res. (2008) pmid: 18199554
88. Reck M, et al. Lancet Respir Med (2019) pmid: 30922878
89. Socinski MA, et al. J Thorac Oncol (2021) pmid: 34311108
90. Socinski MA, et al. N. Engl. J. Med. (2018) pmid: 29863955
91. Lu et al., 2021; ESMO Abstract VP9-2021
92. Vallee A, et al. Int. J. Oncol. (2013) pmid: 23934203
93. Imielinski M, et al. Cell (2012) pmid: 22980975
94. Nature (2014) pmid: 25079552
95. Nature (2012) pmid: 22960745
96. Watzka SB, et al. Eur J Cardiothorac Surg (2010) pmid: 20353893
97. Liang Z, et al. BMC Cancer (2010) pmid: 20637128
98. Grob TJ, et al. Lung Cancer (2013) pmid: 23238037
99. Park S, et al. Histol. Histopathol. (2012) pmid: 22207554
100. Dobashi Y, et al. Hum. Pathol. (2011) pmid: 21040950
101. Ludovini V, et al. Cancer Chemother. Pharmacol. (2013) pmid: 23314677
102. Skrzypski M, et al. Clin Lung Cancer (2013) pmid: 23870818
103. Kim SH, et al. Histol. Histopathol. (2012) pmid: 22419022
104. Lee JS, et al. Ann. Surg. Oncol. (2013) pmid: 23525704
105. Oakley GJ, et al. J Thorac Oncol (2011) pmid: 21587084
106. Marks JL, et al. J Thorac Oncol (2008) pmid: 18303429
107. Izar B, et al. Ann. Thorac. Surg. (2013) pmid: 23932319
108. Hayasaka et al., 2018; WCLC Abstract P3.16-03
109. Ciardiello F, et al. N. Engl. J. Med. (2008) pmid: 18337605
110. Lynch TJ, et al. N. Engl. J. Med. (2004) pmid: 15118073
111. Paez JG, et al. Science (2004) pmid: 15118125
112. Pao W, et al. Proc. Natl. Acad. Sci. U.S.A. (2004) pmid: 15329413
113. Yang JC, et al. Lancet Oncol. (2015) pmid: 25589191
114. Wu YL, et al. Lancet Oncol. (2017) pmid: 28958502
115. Foster SA, et al. Cancer Cell (2016) pmid: 26996308
116. Tanaka K, et al. Oncotarget (2017) pmid: 28978102
117. Gazdar A, et al. J Thorac Oncol (2014) pmid: 24736066
118. Bell DW, et al. Nat. Genet. (2005) pmid: 16258541
119. Oxnard GR, et al. J Thorac Oncol (2012) pmid: 22588155
120. Godin-Heymann N, et al. Cancer Res. (2007) pmid: 17671201
121. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
122. Gao J, et al. Sci Signal (2013) pmid: 23550210
123. Trowbridge JJ, et al. Nat. Genet. (2011) pmid: 22200773
124. Prog Mol Biol Transl Sci (2011) pmid: 21507354
125. Yang J, et al. Mol Med Rep () pmid: 21887466
126. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
127. Daskalos A, et al. Cancer (2011) pmid: 21351083
128. Fabbri M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17890317
129. Gao Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22011581
130. Kim MS, et al. APMIS (2013) pmid: 23031157
131. Yan XJ, et al. Nat. Genet. (2011) pmid: 21399634
132. Holz-Schietinger C, et al. J. Biol. Chem. (2012) pmid: 22722925
133. Metzeler KH, et al. Leukemia (2012) pmid: 22124213
134. Abdel-Wahab O, et al. Blood (2013) pmid: 23640996
135. Chen ZX, et al. J. Cell. Biochem. (2005) pmid: 15861382
136. Guo X, et al. Nature (2015) pmid: 25383530
137. Sandoval JE, et al. J. Biol. Chem. (2019) pmid: 30705090
138. Zhang ZM, et al. Nature (2018) pmid: 29414941
139. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
140. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
141. Xie M, et al. Nat. Med. (2014) pmid: 25326804
142. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
143. Severson EA, et al. Blood (2018) pmid: 29678827
144. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
145. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
146. Chabon JJ, et al. Nature (2020) pmid: 32269342
147. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
148. Bantscheff M, et al. Nat. Biotechnol. (2007) pmid: 17721511
149. Melnick JS, et al. Proc. Natl. Acad. Sci. U.S.A. (2006) pmid: 16492761
150. Boyd AW, et al. Nat Rev Drug Discov (2014) pmid: 24378802
151. Barquilla A, et al. Annu. Rev. Pharmacol. Toxicol. (2015) pmid: 25292427
152. Nature (2014) pmid: 25079317
153. Mäki-Nevala S, et al. Genes Chromosomes Cancer (2013) pmid: 24123310
154. Bonifaci N, et al. PLoS ONE (2010) pmid: 21124932
155. Wang JD, et al. Oncology (2007) pmid: 18424888
156. Sheng Z, et al. Pathobiology (2008) pmid: 18931529
157. Zhou S, et al. Int J Clin Exp Pathol (2014) pmid: 25120806
158. Wang H, et al. Int J Clin Exp Pathol (2014) pmid: 24427352
159. Senchenko VN, et al. Epigenetics (2013) pmid: 23478628

160. Dmitriev AA, et al. Epigenetics (2012) pmid: 22491060
161. Kuang SQ, et al. Blood (2010) pmid: 20061560
162. Berardi AC, et al. Anticancer Res. () pmid: 18507018
163. Teng L, et al. Neuro-oncology (2013) pmid: 24121831
164. Yuan Y, et al. Asian Pac. J. Cancer Prev. (2014) pmid: 24606480
165. Shi G, et al. Cell Res. (2010) pmid: 20697431
166. Cell (2008) pmid: 18394988
167. Nat. Rev. Cancer (2010) pmid: 20179713
168. Yen WC, et al. Clin. Cancer Res. (2015) pmid: 25934888
169. Ferrarotto et al., 2020; ESMO Abstract 919MO
170. Zhang K, et al. Clin. Cancer Res. (2020) pmid: 32241817
171. Ding L, et al. Nature (2008) pmid: 18948947
172. Mimae T, et al. Clin. Cancer Res. (2012) pmid: 22190591
173. Penton AL, et al. Semin. Cell Dev. Biol. (2012) pmid: 22306179
174. Kopan R, et al. Cell (2009) pmid: 19379690
175. Pancewicz J, et al. BMC Cancer (2011) pmid: 22128846
176. Sakata-Yanagimoto M, et al. Curr. Top. Microbiol. Immunol. (2012) pmid: 22695918
177. Kiel MJ, et al. J. Exp. Med. (2012) pmid: 22891276
178. Egloff AM, et al. Clin. Cancer Res. (2012) pmid: 22773520
179. Wang NJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22006338
180. Beà S, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 24145436
181. McDaniell R, et al. Am. J. Hum. Genet. (2006) pmid: 16773578
182. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
183. Supernat A, et al. Oncol Lett (2012) pmid: 23205091
184. Xu H, et al. Breast Cancer Res. (2011) pmid: 21255398
185. Sharaf R, et al. Genome Med (2022) pmid: 35227290
186. Su XA, et al. Genes Dev (2021) pmid: 33766983
187. Deb S, et al. Br. J. Cancer (2014) pmid: 24548858
188. Xu H, et al. Nat. Rev. Cancer (2011) pmid: 21326324
189. Hill VK, et al. Biochim. Biophys. Acta (2016) pmid: 27207471
190. Solomon DA, et al. BMB Rep (2014) pmid: 24856830
191. Bauerschmidt C, et al. Nucleic Acids Res. (2010) pmid: 19906707
192. Yun J, et al. Nucleic Acids Res. (2016) pmid: 26420833
193. Gelot C, et al. Nucleus (2016) pmid: 27326661
194. Yan M, et al. Breast Cancer Res. (2012) pmid: 22537934
195. Sofueva S, et al. EMBO J. (2013) pmid: 24185899
196. Deng Z, et al. EMBO J. (2012) pmid: 23010778
197. Yun J, et al. EMBO Rep. (2016) pmid: 27466323
198. Mahmood SF, et al. Carcinogenesis (2014) pmid: 24148822
199. Ito S, et al. Nature (2010) pmid: 20639862
200. Guo JU, et al. Cell (2011) pmid: 21496894
201. Iyer LM, et al. Cell Cycle (2009) pmid: 19411852
202. Ko M, et al. Nature (2010) pmid: 21057493
203. Yang H, et al. Oncogene (2013) pmid: 22391558
204. Hu L, et al. Cell (2013) pmid: 24315485
205. Wang Y, et al. Mol. Cell (2015) pmid: 25601757
206. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
207. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
208. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
209. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
210. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
211. Xu L, et al. Mol. Med. (2001) pmid: 11713371
212. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
213. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
214. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
215. Hajdenberg et al., 2012; ASCO Abstract e15010
216. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
217. Moore et al., 2019; ASCO Abstract 5513
218. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
219. Oza et al., 2015; ASCO Abstract 5506
220. Lee J, et al. Cancer Discov (2019) pmid: 31315834
221. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
222. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
223. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
224. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
225. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
226. Gourley et al., 2016; ASCO Abstract 5571
227. Kwok M, et al. Blood (2016) pmid: 26563132
228. Boudny M, et al. Haematologica (2019) pmid: 30975914
229. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
230. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
231. Mogi A, et al. J. Biomed. Biotechnol. (2011) pmid: 21331359
232. Tekpli X, et al. Int. J. Cancer (2013) pmid: 23011884
233. Vignot S, et al. J. Clin. Oncol. (2013) pmid: 23630207
234. Maeng CH, et al. Anticancer Res. (2013) pmid: 24222160
235. Cortot AB, et al. Clin Lung Cancer (2014) pmid: 24169260
236. Itakura M, et al. Br. J. Cancer (2013) pmid: 23922113
237. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
238. Dong ZY, et al. Clin. Cancer Res. (2017) pmid: 28039262
239. Seo JS, et al. Genome Res. (2012) pmid: 22975805
240. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
241. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
242. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
243. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
244. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
245. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
246. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
247. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
248. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
249. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
250. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
251. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
252. Lalloo F, et al. Lancet (2003) pmid: 12672316
253. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
254. Alanazi A, et al. Lung Cancer Manag (2020) pmid: 33318755
255. Kim et al., 2021; DOI: 10.1200/PO.20.00296
256. Wang J, et al. Int. J. Cancer (2019) pmid: 30255937
257. Ramalingam SS, et al. N. Engl. J. Med. (2019) pmid: 31751012
258. Herbst et al., 2020; ASCO Abstract LBA5
259. Mok TS, et al. N. Engl. J. Med. (2017) pmid: 27959700
260. Auliac et al., 2018; WCLC Abstract P1.13-09
261. Kang et al., 2018; WCLC Abstract MA08.07
262. Miyauchi E, et al. J Thorac Oncol (2017) pmid: 28434520
263. Yoshida H, et al. J Thorac Oncol (2017) pmid: 28291724
264. Kenmotsu et al., 2021; ESMO Abstract LBA44
265. Soo et al., 2021; ESMO Abstract VP3-2021
266. Oxnard GR, et al. Ann. Oncol. (2020) pmid: 32139298
267. Wu YL, et al. Lancet Oncol. (2014) pmid: 24439929
268. Passaro et al., 2019; ELCC Abstract 1150
269. Audet et al., 2013; ASCO Abstract 6041
270. De Grève J, et al. Lung Cancer (2015) pmid: 25682316
271. Yang JC, et al. Lancet Oncol. (2015) pmid: 26051236
272. He et al., 2017, 27511219
273. Yang JC, et al. J Thorac Oncol (2020) pmid: 31931137
274. Chang et al., 2018; WCLC Abstract P1.01-11
275. Janjigian YY, et al. Cancer Discov (2014) pmid: 25074459
276. Ribeiro Gomes J, et al. Onco Targets Ther (2015) pmid: 26056478
277. Castellanos EH, et al. Clin Lung Cancer (2015) pmid: 25842367
278. Lau SC, et al. Clin Lung Cancer (2019) pmid: 31178389
279. Paz-Ares L, et al. Ann. Oncol. (2017) pmid: 28426106
280. Thongprasert S, et al. Lung Cancer Manag (2019) pmid: 31807143
281. Januszewski et al., 2018; IASLC WCLC Abstract P1.13-17
282. Suzuki et al., 2018; IASLC WCLC Abstract P1.01-92
283. Chang et al., 2018; IASLC WCLC Abstract P1.01-11
284. Llinás-Quintero N, et al. Case Rep Oncol Med (2019) pmid: 31637072
285. Miller VA, et al. Lancet Oncol. (2012) pmid: 22452896
286. Chen X, et al. Lung Cancer (2013) pmid: 23664448
287. Katakami N, et al. J. Clin. Oncol. (2013) pmid: 23816963
288. Landi L, et al. Clin Lung Cancer (2014) pmid: 25242668
289. Horn L, et al. Lung Cancer (2017) pmid: 29110849
290. Yamamoto N, et al. Adv Ther (2020) pmid: 31863283
291. Soria JC, et al. Lancet Oncol. (2015) pmid: 26156651
292. Dziadziuszko R, et al. J Thorac Oncol (2019) pmid: 30825613
293. Lai WV, et al. Eur. J. Cancer (2019) pmid: 30685684
294. Greulich H, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22908275
295. Gow CH, et al. J Thorac Oncol (2015) pmid: 26134234
296. Mazières J, et al. Ann. Oncol. (2016) pmid: 26598547
297. Mazières J, et al. J. Clin. Oncol. (2013) pmid: 23610105
298. De Grève J, et al. Lung Cancer (2012) pmid: 22325357
299. Li BT, et al. Lung Cancer (2015) pmid: 26559459
300. Costa DB, et al. J Thorac Oncol (2016) pmid: 26964772
301. Yuan B, et al. Front Oncol (2020) pmid: 32477948
302. Fang W, et al. Oncologist (2019) pmid: 31748336
303. Schuler M, et al. Ann. Oncol. (2016) pmid: 26646759
304. Lemos H, et al. Expert Rev Clin Immunol (2015) pmid: 25521938
305. Takahashi T, et al. Invest New Drugs (2012) pmid: 22249430
306. Opsomer RJ, et al. Acta Urol Belg (1985) pmid: 2986437
307. Wu et al., 2018; WCLC abstract MA26.11
308. Ramalingam SS, et al. Ann. Oncol. (2016) pmid: 26768165
309. van Geel RMJM, et al. Br. J. Cancer (2020) pmid: 32147669
310. Jänne PA, et al. J Thorac Oncol (2016) pmid: 26899759
311. Cappuzzo F, et al. Lancet Oncol. (2010) pmid: 20493771
312. Zhong WZ, et al. J. Clin. Oncol. (2019) pmid: 31194613
313. Petrelli F, et al. Clin Lung Cancer (2012) pmid: 22056888
314. Truini A, et al. Clin. Cancer Res. (2019) pmid: 31182434
315. Leon et al., 2014; doi.org/10.1093/annonc/mdu349.52
316. Lee CK, et al. J. Natl. Cancer Inst. (2017) pmid: 28376144
317. Yang JJ, et al. Br. J. Cancer (2017) pmid: 28103612
318. Zhou Q, et al. Cancer Cell (2021) pmid: 34388377

319. Kawashima Y, et al. Lancet Respir Med (2022) pmid: 34454653
320. Saito H, et al. Lancet Oncol (2019) pmid: 30975627
321. Piccirillo et al., 2021; ESMO Abstract 12070
322. Faehling M, et al. J Cancer Res Clin Oncol (2018) pmid: 29687154
323. Nakagawa K, et al. Lancet Oncol. (2019) pmid: 31591063
324. Han JY, et al. J. Clin. Oncol. (2012) pmid: 22370314
325. Maemondo M, et al. N. Engl. J. Med. (2010) pmid: 20573926
326. Mitsudomi T, et al. Lancet Oncol. (2010) pmid: 20022809
327. Mok TS, et al. N. Engl. J. Med. (2009) pmid: 19692680
328. Qi WX, et al. Curr Med Res Opin (2015) pmid: 25329826
329. Zhao H, et al. J Thorac Oncol (2015) pmid: 25546556
330. Baik CS, et al. J Thorac Oncol (2015) pmid: 26398831
331. Yoshioka H, et al. Ann. Oncol. (2019) pmid: 31553438
332. Fukuoka M, et al. J. Clin. Oncol. (2011) pmid: 21670455
333. Sutiman N, et al. J Thorac Oncol (2017) pmid: 27908825
334. Noronha V, et al. J. Clin. Oncol. (2019) pmid: 31411950
335. Hosomi Y, et al. J. Clin. Oncol. (2020) pmid: 31682542
336. Creelan BC, et al. Br J Cancer (2021) pmid: 33012782