FOUNDATIONONE® LIQUID CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma

REPORT DATE

COUNTRY CODE
ES

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	PHYSICIAN	SPECIMEN
DISEASE Lung adenocarcinoma	ORDERING PHYSICIAN	SPECIMEN ID
NAME	MEDICAL FACILITY	SPECIMEN TYPE
DATE OF BIRTH	ADDITIONAL RECIPIENT	DATE OF COLLECTION
SEX	MEDICAL FACILITY ID	SPECIMEN RECEIVED
MEDICAL RECORD #	PATHOLOGIST	

Genomic Signatures

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

Gene Alterations

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

EGFR L858R
APC P1634L
CTNNB1 S37F
PTEN splice site 254-2A>T
CDKN2A/B p16INK4a H83Y and p14ARF A97V
TP53 P177L, C275F, splice site 782+1G>A

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Afatinib** (p. 11), **Dacomitinib** (p. 12), **Erlotinib** (p. 12), **Gefitinib** (p. 13), **Osimertinib** (p. 13)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 15)

GENOMIC SIGNATURES

Blood Tumor Mutational Burden
- 1 Muts/Mb

Microsatellite status
- MSI-High Not Detected

Tumor Fraction
- Elevated Tumor Fraction Not Detected

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Genomic Signatures section

MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).

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 Genomic Signatures section).

GENE ALTERATIONS		VAF %
EGFR -	L858R	1.4%

10 Trials see p. 17

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Afatinib	1	None
Dacomitinib	1	
Erlotinib	1	
Gefitinib	1	
Osimertinib	1	

☐ *NCCN category*

Electronically signed by Shari Brown, M.D. |
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GENE ALTERATIONS		VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
APC -	P1634L	50.2%	None	None
3 Trials see p. 15				
CTNNB1 -	S37F	0.16%	None	None
5 Trials see p. 16				
PTEN -	splice site 254-2A>T	2.0%	None	None
10 Trials see p. 19				

☐ *NCCN category*

GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

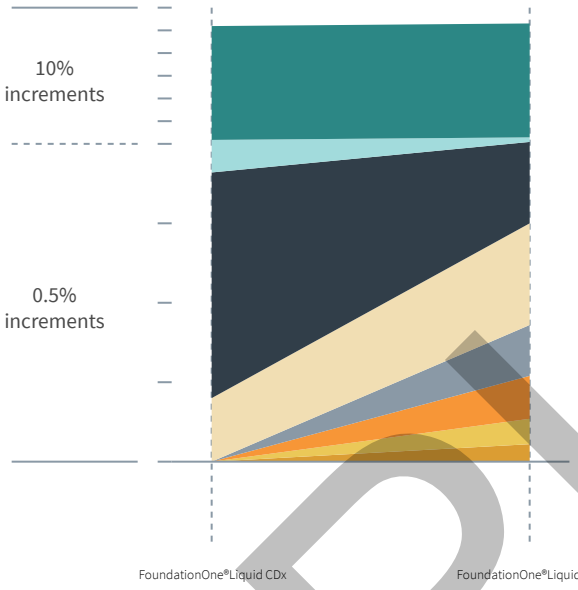
For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Gene Alterations section.

CDKN2A/B - p16INK4a H83Y and p14ARF A97V ..... p. 9 ***TP53*** - P177L, C275F, splice site 782+1G>A ..... p. 10

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 through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally in some EU Member States but may not be available in your Member State: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, and Triptorelin. The Summary of Product Characteristics of EU-approved therapies are available at https://www.ema.europa.eu/en/medicines. The information available on EMA's website is updated in regular intervals but may not reflect the current status at any time. 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.

Variant Allele Frequency Percentage (VAF%)



HISTORIC PATIENT FINDINGS		[redacted] VAF%	[redacted] VAF%	CHANGE FROM PREV.
Blood Tumor Mutational Burden		1 Muts/Mb	1 Muts/Mb	-
Microsatellite status		MSI-High Not Detected	MSI-High Not Detected	-
Tumor Fraction		Elevated Tumor Fraction Not Detected	Elevated Tumor Fraction Not Detected	-
EGFR	L858R	1.4%	1.4%	0%
APC	P1634L	50.2%	50.2%	0%
CTNNB1	S37F	Not Detected	0.16%	+0.16%
PTEN	splice site 254-2A>T	1.9%	2.0%	+0.10%
CDKN2A/B	p16INK4a H83Y and p14ARF A97V	Not Detected	0.32%	+0.32%
TP53	P177L	Not Detected	0.27%	+0.27%
	splice site 782+1G>A	0.40%	0.64%	+0.24%
	C275F	Not Detected	0.11%	+0.11%

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

GENOMIC SIGNATURE

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.

GENOMIC SIGNATURE

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
L858R

TRANSCRIPT ID
NM_005228

CODING SEQUENCE EFFECT
2573T>G

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 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[50-53] . 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[54]. 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[55-56]. 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[57]. 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[58]. OR was observed in a numerically higher proportion of patients with the EGFR T790M mutation than those without this mutation[58].

— 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)[59-61] or sintilimab plus bevacizumab biosimilar plus cisplatin and pemetrexed (PFS HR 0.46 compared with chemotherapy alone)[62].

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[63-65] and in 4% of lung squamous cell carcinomas[66]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[67-72]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[73-74]. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[75-76]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[77] or resected Stage 1 NSCLC[78].

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[79]. EGFR L858 is located in the kinase domain and is encoded by exon 21. EGFR L858R has been characterized as activating[80-82] and patients with the L858R mutation have been shown to be sensitive to EGFR tyrosine kinase inhibitors, such as erlotinib, gefitinib[80-82], and afatinib[83].

GENE
APC

ALTERATION
P1634L

TRANSCRIPT ID
NM_000038

CODING SEQUENCE EFFECT
4901C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs[84], and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP[85-86]. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days[87]; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386[88-89]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In the TCGA datasets, APC mutations have been reported in 3.9% of lung adenocarcinomas[65] and 4.5% of lung squamous cell carcinoma samples analyzed[66]. Studies of APC in lung cancer have reported mutations in 5-7% of non-small cell lung cancer (NSCLC) tumors examined[90-91]. In contrast, loss of heterozygosity at the APC/MCC locus has been reported in up to 68% (17/25) of NSCLC, with a higher incidence in squamous cell carcinomas compared to adenocarcinomas[92-93]. Hypermethylation of APC in NSCLC tumors has been reported in a number of studies[94-97]; hypermethylation and lower APC mRNA expression have been associated with poorer survival in patients with NSCLC[93,98]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[99].

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[100]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[101-103]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[104], and in the appropriate clinical context germline testing of APC is recommended.

GENE
CTNNB1

ALTERATION
S37F

TRANSCRIPT ID
NM_001904

CODING SEQUENCE EFFECT
110C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Mutation or activation of CTNNB1 signaling has been shown to increase mTOR signaling, promote tumorigenesis, and respond to mTOR inhibition in preclinical studies[105-107]. Small studies have reported clinical benefit following treatment of everolimus combined with other targeted agents for patients with CTNNB1-mutated hepatocellular carcinoma[108-109] or endometrial carcinoma[110]. In preclinical studies, CTNNB1 activating mutations have been shown to increase expression of WNT pathway member DKK1, which may promote tumor cell proliferation and immune evasion[111-113]. A Phase 1 trial of DKK1-targeting antibody DKN-01 in combination with paclitaxel in esophageal cancer reported a PR rate in 2 out of 4 patients and SD rate of in 1 out of 4 patients with CTNNB1 activating mutations, compared with 24% (10/41) PR and 37% (15/41) SD in unselected patients[114]. Multiple preclinical studies in cancer models harboring CTNNB1 mutation or beta-catenin pathway activation have reported activation of the NOTCH pathway and sensitivity to pharmacologic inhibition of NOTCH signaling by gamma-secretase inhibitors[115-118]. Phase 1 and 2 clinical trials of gamma-secretase inhibitor PF-03084014 have shown high response rates in patients with desmoid tumors, which are driven by activating CTNNB1 mutations in the majority of cases[119-120], suggesting CTNNB1-mutated tumors may be sensitive to gamma-secretase inhibitors. Although WNT pathway inhibitors have been explored preclinically in CTNNB1-mutated cells, clinical data supporting this therapeutic approach are lacking[106,121-123].

FREQUENCY & PROGNOSIS

CTNNB1 mutations have been reported in 4% of lung adenocarcinomas[65] and in 2% of lung squamous cell carcinomas[66]. One study reported aberrant beta-catenin immunostaining in 47% of lung adenocarcinomas[124]. Aberrant beta-catenin expression has been associated with poor prognosis in patients with lung adenocarcinoma and other non-small cell lung carcinomas[125-127]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[99].

FINDING SUMMARY

CTNNB1 encodes beta-catenin, a key downstream component of the WNT signaling pathway. Beta-catenin interacts with cadherin to regulate cell-cell adhesion; as a component of the WNT pathway, it also plays a role in development, cell proliferation, and cell differentiation[128]. CTNNB1 exon 3 mutations, such as observed here, lead to increased beta-catenin protein stability and activation of the WNT pathway, and are considered to be activating[129-147].

GENE
PTEN

ALTERATION
splice site 254-2A>T

TRANSCRIPT ID
NM_000314

CODING SEQUENCE EFFECT
254-2A>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[148-151]. Across various tissues, most clinical studies have not observed an association between PTEN deficiency and response to inhibitors of the PI3K-AKT-mTOR pathway. However, limited studies in prostate cancer[152-155], renal cell carcinoma[156], breast cancer[157-158], and colorectal cancer[159] have reported an association between PTEN deficiency and response to inhibitors targeting the PI3K-AKT-mTOR pathway. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[160-164], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[165], ovarian cancer[166], uterine leiomyosarcoma[167], and endometrial cancer[164] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[168-169].

FREQUENCY & PROGNOSIS

Studies have reported PTEN mutation in 4.5% of non-small cell lung cancer (NSCLC) cases[170], with higher incidence reported in lung squamous cell carcinoma (10-11%)[66,170] compared with lung adenocarcinoma (1-2.5%)[64-65,91,170]. PTEN loss has been reported in 9.9% of lung SCC and <1% of lung NSCLC cases[171-172]. Loss of PTEN expression by IHC was reported in up to 35% of NSCLC cases in one study, with several studies reporting more frequent loss of PTEN in squamous cell lung carcinoma compared to lung adenocarcinoma[173-176]. Loss of PTEN protein expression has been identified as a marker of poor prognosis in NSCLC[173,175].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[149]. Alterations such as seen here may disrupt PTEN function or expression[177-218].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[219-220]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[219,221]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[219]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
CDKN2A/B

ALTERATION
p16INK4a H83Y and p14ARF A97V

TRANSCRIPT ID
NM_000077

CODING SEQUENCE EFFECT
247C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[222-223], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[224-230]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[231-232], the clinical relevance of p14ARF as a predictive biomarker is not clear. Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[233-236].

FREQUENCY & PROGNOSIS

CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[65]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[66]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples[66,237-242]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[239,243-245].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[246-247]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[238,248]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[249-250]. One or more alterations observed here are predicted to result in p16INK4a loss of function[251-272]. One or more alterations seen here have been observed in the context of cancer but have not been characterized and their effect on p14ARF function is unclear.

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[273]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[274-275]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[276-278]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[279-281]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
TP53

ALTERATION
P177L, C275F, splice site 782+1G>A

TRANSCRIPT ID
NM_000546, NM_000546, NM_000546

CODING SEQUENCE EFFECT
530C>T, 824G>T, 782+1G>A

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[282-285], or p53 gene therapy and immunotherapeutics such as SGT-53[286-290] and ALT-801[291]. 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[292]. 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[293]. 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[294]. 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[295]. 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[296]. 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[297]. 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[298]. 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[290]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[299-301]. 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[302]. 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[303-304]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[305-306]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[65-66,241,307-311], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2022)[64-66,312]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2022)[171-172]. 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[313]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[314].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[315]. Alterations such as seen here may disrupt TP53 function or expression[316-320].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[321-323], including sarcomas[324-325]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[326] to 1:20,000[325]. 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[327]. 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[328-333]. 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[328-329]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[334]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[332,335-336]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Afatinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is available in the EU to treat patients with advanced non-small cell lung cancer (NSCLC) and activating EGFR mutations and for the treatment of patients with advanced 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[41-42,337-338] , whereas data for patients with other tumor types are limited[44-49,339] .

SUPPORTING DATA

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[41,337,340-343] . 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)[41,337] . 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[83]. 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)[340]. 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[341]. 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[342]. 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[343] 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[344]. 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[345]. 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[346]. 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%[347-352] ; however, DCRs of more than 50% have been observed[351]. 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[353] or osimertinib[354], 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[41,83,337,341,343,345,355] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[351,356-366] . 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[355]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[367].

Dacomitinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

Dacomitinib is a second-generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is available in the EU for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) with EGFR activating 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[41-42,337-338] , whereas data for patients with other tumor types are limited[44-49,339] . Patients with untreated advanced NSCLC and EGFR L858R mutations achieved an ORR of 73% (68/93)[368] and a median OS of 32.5 months with dacomitinib[42].

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)[368-369] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[370]. 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)[371]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[372-374] . 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[375]. 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)[373]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[376].

Erlotinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

Erlotinib is an EGFR tyrosine kinase inhibitor. It is available in the EU to treat advanced non-small cell lung cancer (NSCLC) as first-line therapy or switch maintenance therapy for patients with EGFR-activating mutations and as second-line therapy for patients who have progressed on prior chemotherapy. Erlotinib is also available in combination with gemcitabine to treat metastatic 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[39,377-379] .

SUPPORTING DATA

For patients with EGFR-mutated non-small cell lung cancer (NSCLC), the Phase 3 EURTAC trial improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37), though OS was not prolonged (22.9 vs 19.6 months, HR=0.92)[39,380] . This study and meta-analyses attribute the lack of OS benefit to the effectiveness of post-progression salvage therapy in the control arm[381]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[382]. 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)[383], the NEJ026 trial for Japanese patients (16.9 vs. 13.3 months, HR=0.605)[384-385] , and the international BEVERLY trial (15.4 vs. 9.7 months, HR=0.60)[386]; 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[377,387] . 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[378]. 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)[388].

Gefitinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

Gefitinib is an EGFR tyrosine kinase inhibitor available in the EU to treat patients with advanced non-small cell lung cancer (NSCLC) with activating EGFR mutations. 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[379,389-394] , and responses have been reported for patients with EGFR-rearranged NSCLC[395-396] .

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[391,397] and East Asian patients[392,398] 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)[399]. 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[400-401] . 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[402].

Osimertinib

Assay findings association

EGFR
L858R

AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR tyrosine kinase inhibitor (TKI) that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is available in the EU in various treatment settings for patients with non-small cell lung cancer (NSCLC) whose tumors harbor EGFR T790M mutations or activating mutations, including EGFR exon 19 deletions and exon 21 L858R 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[43,395,403-405] . 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[403].

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)[403,406] . 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)[407]. 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). 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)[408]. 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)[409]. 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[410].

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. 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. Therapies listed in this report may not be complete and/or exhaustive. In particular, the listed therapies are limited to EMA or nationally approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be EMA or nationally 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 EMA or an EU Member State nationally. 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
APC

ALTERATION
P1634L

RATIONALE
Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT03264664

PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS
CBP, Beta-catenin

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

NCT03833700

PHASE 1

A Study of E7386 in Participants With Advanced Solid Tumor Including Colorectal Cancer (CRC)

TARGETS
CBP, Beta-catenin

LOCATIONS: Fukuoka (Japan), Kashiwa (Japan), Chuo Ku (Japan), Nagaizumi-cho (Japan)

NCT04008797

PHASE 1

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

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

LOCATIONS: Osakasayama (Japan), Kashiwa (Japan), Chuo-Ku (Japan)

GENE
CTNNB1

ALTERATION
S37F

RATIONALE
Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive to mTOR inhibitors.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China), Chongqing (China)

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

GENE
EGFR

ALTERATION
L858R

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

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: A Coruña (Spain), Porto (Portugal), Burgos (Spain), Majadahonda (Spain), Madrid (Spain), Pamplona (Spain), Lisboa (Portugal), Zaragoza (Spain), Seville (Spain), Valencia (Spain)

NCT03944772

PHASE 2

Phase 2 Platform Study in Patients With Advanced Non-Small Lung Cancer Who Progressed on First-Line Osimertinib Therapy (ORCHARD)

TARGETS
EGFR, PD-L1, RET, MET, ALK

LOCATIONS: A Coruña (Spain), Madrid (Spain), Sevilla (Spain), Barcelona (Spain), Maastricht (Netherlands), Rotterdam (Netherlands), Amsterdam (Netherlands), Nijmegen (Netherlands), Drammen (Norway), Oslo (Norway)

NCT02609776

PHASE 1

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

TARGETS
MET, EGFR

LOCATIONS: A Coruña (Spain), Santander (Spain), Madrid (Spain), Bordeaux (France), Seville (Spain), Saint-Herblain Cedex (France), Malaga (Spain), Barcelona (Spain), Villejuif Cedex (France), Paris (France)

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

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: Madrid (Spain), Bordeaux (France), Seville (Spain), Poitiers (France), Barcelona (Spain), Villejuif Cedex (France), Paris (France), Saint Mande (France), Lyon Cedex 8 (France), 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: Bayonne (France), Pau (France), Bordeaux (France), Rennes (France), Toulouse (France), Limoges (France), Tours (France), Le Mans (France), Caen (France), Orléans (France)

CLINICAL TRIALS

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: Borddeaux Cedex (France), Nantes Cedex 01 (France), Creteil (France), Rouen (France), New York, Toronto (Canada), Pennsylvania, North Carolina, Tennessee, Missouri

NCT03865511

PHASE 2

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

TARGETS
EGFR

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

NCT04413201

PHASE 4

AFAMOSI: Efficacy and Safety of Afatinib Followed by Osimertinib Compared to Osimertinib in Patients With EGFRmutated/T790M Mutation Negative Nonsquamous NSCLC

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Konstanz (Germany), Löwenstein (Germany), Offenbach (Germany), Immenstadt (Germany), Gießen (Germany), Hamm (Germany), München (Germany), Regensburg (Germany), Bremen (Germany), Hamburg (Germany)

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, New York, New Jersey, Virginia, Michigan, Taichung City (Taiwan), Illinois, Tennessee

GENE
PTEN

ALTERATION
splice site 254-2A>T

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

NCT03739710

PHASE 2

Platform Trial of Novel Regimens Versus Standard of Care (SoC) in Non-small Cell Lung Cancer (NSCLC)

TARGETS
CTLA-4, ICOS, PD-1, TIM-3, PARP

LOCATIONS: Santander (Spain), Madrid (Spain), Badajoz (Spain), Bordeaux Cedex (France), Sevilla (Spain), Málaga (Spain), Barcelona (Spain), Caen Cedex 9 (France), Villejuif Cedex (France), Paris Cedex 05 (France)

NCT04380636

PHASE 3

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

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Pozuelo de Alarcon (Spain), La Roche sur Yon (France), Sevilla (Spain), Brest (France), Valencia (Spain), Málaga (Spain), Barcelona (Spain), Bobigny (France), Marseille (France), Amiens (France)

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Madrid (Spain), Sevilla (Spain), Barcelona (Spain), Sutton (United Kingdom), Cambridge (United Kingdom), Manchester (United Kingdom), Milan (Italy), Modena (Italy), Padova (Italy), Roma (Italy)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Bordeaux (France), Villejuif (France), Sutton (United Kingdom), Oxford (United Kingdom), Coventry (United Kingdom), Cambridge (United Kingdom), Manchester (United Kingdom), Withington (United Kingdom), Massachusetts, New York

NCT04770246

PHASE 2

TAS-117 in Patients With Advanced Solid Tumors Harboring Germline PTEN Mutations

TARGETS
AKT2, AKT1, AKT3

LOCATIONS: Villejuif (France), London (United Kingdom), Vienna (Austria), Pennsylvania, Ohio, Texas, California

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

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

CLINICAL TRIALS

NCT04991480

PHASE 1/2

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

TARGETS
PARP, Pol theta

LOCATIONS: London (United Kingdom), New York, Tennessee, Florida, Oklahoma, Texas

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: London (United Kingdom), Newcastle upon Tyne (United Kingdom), Connecticut, Texas

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT04170153

PHASE 1

M1774 in Participants With Metastatic or Locally Advanced Unresectable Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Sutton (United Kingdom), Newcastle upon Tyne (United Kingdom), Texas

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.

BRIP1
T484I

KLHL6
P555H

MED12
Q2119_Q2120insHQQQ

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 GENOMIC SIGNATURES

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.

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:* The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

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

Genomic signatures and gene alterations 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 genomic signature or gene alteration. 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. Leighl et al., 2021; ESMO Abstract 1192MO
51. Cho et al., 2020; ESMO Abstract 1258O
52. Bauml et al., 2021; ASCO Abstract 9006
53. Shu et al., 2021; ESMO Abstract 1193MO
54. Jänne PA, et al. Cancer Discov (2021) pmid: 34548309
55. Ahn MJ, et al. Lancet Respir Med (2017) pmid: 29056570
56. Yang Z, et al. Sci Transl Med (2016) pmid: 27928026
57. Ahn MJ, et al. Lancet Oncol (2019) pmid: 31587882
58. Lin L, et al. Lung Cancer (2022) pmid: 35248866
59. Reck M, et al. Lancet Respir Med (2019) pmid: 30922878
60. Socinski MA, et al. J Thorac Oncol (2021) pmid: 34311108
61. Socinski MA, et al. N. Engl. J. Med. (2018) pmid: 29863955
62. Lu et al., 2021; ESMO Abstract VP9-2021
63. Vallee A, et al. Int. J. Oncol. (2013) pmid: 23934203
64. Imielinski M, et al. Cell (2012) pmid: 22980975
65. Nature (2014) pmid: 25079552
66. Nature (2012) pmid: 22960745
67. Watzka SB, et al. Eur J Cardiothorac Surg (2010) pmid: 20353893
68. Liang Z, et al. BMC Cancer (2010) pmid: 20637128
69. Grob TJ, et al. Lung Cancer (2013) pmid: 23238037
70. Park S, et al. Histol. Histopathol. (2012) pmid: 22207554
71. Dobashi Y, et al. Hum. Pathol. (2011) pmid: 21040950
72. Ludovini V, et al. Cancer Chemother. Pharmacol. (2013) pmid: 23314677
73. Skrzypski M, et al. Clin Lung Cancer (2013) pmid: 23870818
74. Kim SH, et al. Histol. Histopathol. (2012) pmid: 22419022
75. Lee JS, et al. Ann. Surg. Oncol. (2013) pmid: 23525704
76. Oakley GJ, et al. J Thorac Oncol (2011) pmid: 21587084
77. Marks JL, et al. J Thorac Oncol (2008) pmid: 18303429
78. Izar B, et al. Ann. Thorac. Surg. (2013) pmid: 23932319
79. Ciardiello F, et al. N. Engl. J. Med. (2008) pmid: 18337605
80. Lynch TJ, et al. N. Engl. J. Med. (2004) pmid: 15118073
81. Paez JG, et al. Science (2004) pmid: 15118125
82. Pao W, et al. Proc. Natl. Acad. Sci. U.S.A. (2004) pmid: 15329413
83. Yang JC, et al. Lancet Oncol. (2015) pmid: 25589191
84. Zhan T, et al. Oncogene (2017) pmid: 27617575
85. Jung YS, et al. Exp Mol Med (2020) pmid: 32037398
86. Krishnamurthy N, et al. Cancer Treat Rev (2018) pmid: 29169144
87. Kawazoe et al., 2021; ESMO Abstract 473P
88. Yamada K, et al. Cancer Res (2021) pmid: 33408116
89. Kanda Y, et al. Biochem Biophys Res Commun (2022) pmid: 34837838
90. Ohgaki H, et al. Cancer Lett. (2004) pmid: 15072829
91. Ding L, et al. Nature (2008) pmid: 18948947
92. Sanz-Ortega J, et al. Pathol. Res. Pract. (1999) pmid: 10549031
93. Poursoltan P, et al. Lung Cancer (2012) pmid: 22542170
94. Zhang Y, et al. Cancer Lett. (2011) pmid: 21255913
95. Virmani AK, et al. Clin. Cancer Res. (2001) pmid: 11448917
96. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
97. J. Natl. Cancer Inst. (2014) pmid: 24309006
98. Lu Y, et al. PLoS Med. (2006) pmid: 17194181
99. Luke JJ, et al. Clin Cancer Res (2019) pmid: 30635339
100. Logan CY, et al. Annu. Rev. Cell Dev. Biol. (2004) pmid: 15473860
101. Kerr SE, et al. J Mol Diagn (2013) pmid: 23159591
102. Annu Rev Pathol (2011) pmid: 21090969
103. Kastritis E, et al. Int. J. Cancer (2009) pmid: 18844223
104. Half E, et al. Orphanet J Rare Dis (2009) pmid: 19822006
105. Tanwar PS, et al. Biol. Reprod. (2009) pmid: 19403928
106. Tanwar PS, et al. PLoS ONE (2011) pmid: 21695255
107. Fujishita T, et al. Proc. Natl. Acad. Sci. U.S.A. (2008) pmid: 18768809
108. Bhoori S, et al. J. Hepatol. (2010) pmid: 20347502
109. Janku F, et al. Oncotarget (2014) pmid: 24931142
110. Slomovitz BM, et al. J. Clin. Oncol. (2015) pmid: 25624430
111. Niida A, et al. Oncogene (2004) pmid: 15378020
112. Chamorro MN, et al. EMBO J. (2005) pmid: 15592430
113. Kagey MH, et al. Br. J. Pharmacol. (2017) pmid: 28574171
114. Kagey et al., 2017; AACR Abstract 369
115. Kwon C, et al. Nat. Cell Biol. (2011) pmid: 21841793
116. Arcaroli JJ, et al. Br. J. Cancer (2013) pmid: 23868008
117. Shang H, et al. Cancer (2015) pmid: 26349011
118. Kode A, et al. Nature (2014) pmid: 24429522
119. Kummar et al., 2015; ASCO Abstract 10563
120. Messersmith WA, et al. Clin. Cancer Res. (2015) pmid: 25231399
121. Zhu J, et al. Carcinogenesis (2012) pmid: 22964660
122. Kogan Y, et al. Biochem. J. (2012) pmid: 22356261
123. Lachenmayer A, et al. Clin. Cancer Res. (2012) pmid: 22811581
124. Shi Y, et al. Diagn Pathol (2013) pmid: 23706092
125. Nozawa N, et al. Pathol. Res. Pract. (2006) pmid: 16843618
126. Chiu CG, et al. Am. J. Surg. (2012) pmid: 22402266
127. Kim H, et al. Korean J Pathol (2013) pmid: 23483484
128. Biochem. Biophys. Res. Commun. (2000) pmid: 10679188
129. Anastas JN, et al. Nat. Rev. Cancer (2013) pmid: 23258168
130. Fukuchi T, et al. Cancer Res. (1998) pmid: 9721853
131. Cancer Sci. (2003) pmid: 12824913
132. Takahashi Y, et al. Virchows Arch. (2006) pmid: 16523258
133. Tanaka Y, et al. Cancer Res. (2001) pmid: 11731417
134. Abraham SC, et al. Am. J. Pathol. (2002) pmid: 11943721
135. Austinat M, et al. Mol. Cancer (2008) pmid: 18282277
136. Wu G, et al. Mol. Cell (2003) pmid: 12820959
137. Provost E, et al. Oncogene (2005) pmid: 15829978
138. Curr. Opin. Genet. Dev. (1999) pmid: 10072352
139. Segditsas S, et al. Oncogene (2006) pmid: 17143297
140. Barth AI, et al. J. Cell Biol. (1997) pmid: 9024698
141. Harada N, et al. EMBO J. (1999) pmid: 10545105
142. Hsu SC, et al. Mol. Cell. Biol. (1998) pmid: 9671490
143. Breuhahn K, et al. J. Pathol. (2008) pmid: 18491352
144. Soon PS, et al. Oncologist (2008) pmid: 18515740
145. Tacon LJ, et al. Oncologist (2011) pmid: 21212436
146. Simon DP, et al. Mol. Cell. Endocrinol. (2012) pmid: 22266195
147. Hirotsu Y, et al. Hepatol. Res. (2016) pmid: 26850916
148. Courtney KD, et al. J. Clin. Oncol. (2010) pmid: 20085938
149. Simpson L, et al. Exp. Cell Res. (2001) pmid: 11237521
150. Patnaik A, et al. Ann. Oncol. (2016) pmid: 27672108
151. Milella M, et al. Sci Rep (2017) pmid: 28220839
152. Templeton AJ, et al. Eur. Urol. (2013) pmid: 23582881
153. Sweeney C, et al. Lancet (2021) pmid: 34246347
154. de Bono JS, et al. Clin. Cancer Res. (2019) pmid: 30037818
155. Saura C, et al. Cancer Discov (2017) pmid: 27872130
156. Voss MH, et al. Clin. Cancer Res. (2018) pmid: 30327302
157. André F, et al. J. Clin. Oncol. (2016) pmid: 27091708
158. Schmid P, et al. J. Clin. Oncol. (2019) pmid: 31841354

159. Weldon Gilcrease G, et al. Invest New Drugs (2019) pmid: 30302599
160. Mendes-Pereira AM, et al. EMBO Mol Med (2009) pmid: 20049735
161. Shen Y, et al. Clin. Cancer Res. (2013) pmid: 23881923
162. Chatterjee P, et al. PLoS ONE (2013) pmid: 23565244
163. McCormick A, et al. Int. J. Gynecol. Cancer (2016) pmid: 26905328
164. Forster MD, et al. Nat Rev Clin Oncol (2011) pmid: 21468130
165. Eikesdal HP, et al. Ann Oncol (2021) pmid: 33242536
166. Dougherty et al., 2014; ASCO Abstract 5536
167. Pan M, et al. Perm J (2021) pmid: 33970096
168. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
169. Romero I, et al. Gynecol Oncol (2020) pmid: 32988624
170. Jin G, et al. Lung Cancer (2010) pmid: 20018398
171. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
172. Gao J, et al. Sci Signal (2013) pmid: 23550210
173. O'Byrne KJ, et al. Lancet Oncol. (2011) pmid: 21782507
174. Spoerke JM, et al. Clin. Cancer Res. (2012) pmid: 23136191
175. Yanagawa N, et al. J Thorac Oncol (2012) pmid: 22982652
176. Cumberbatch M, et al. Clin. Cancer Res. (2014) pmid: 24284056
177. Campbell RB, et al. J. Biol. Chem. (2003) pmid: 12857747
178. Rodríguez-Escudero I, et al. Hum. Mol. Genet. (2011) pmid: 21828076
179. He X, et al. Cancer Res. (2013) pmid: 23475934
180. Han SY, et al. Cancer Res. (2000) pmid: 10866302
181. Myers MP, et al. Proc. Natl. Acad. Sci. U.S.A. (1998) pmid: 9811831
182. Pradella LM, et al. BMC Cancer (2014) pmid: 24498881
183. Kim JS, et al. Mol. Cell. Biol. (2011) pmid: 21536651
184. Denning G, et al. Oncogene (2007) pmid: 17213812
185. Hlobilkova A, et al. Anticancer Res. () pmid: 16619501
186. Redfern RE, et al. Protein Sci. (2010) pmid: 20718038
187. Shenoy S, et al. PLoS ONE (2012) pmid: 22505997
188. Wang Y, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19329485
189. Okumura K, et al. J. Biol. Chem. (2006) pmid: 16829519
190. Lee JO, et al. Cell (1999) pmid: 10555148
191. Maxwell GL, et al. Cancer Res. (1998) pmid: 9635567
192. Risinger JI, et al. Clin. Cancer Res. (1998) pmid: 9865913
193. Kato H, et al. Clin. Cancer Res. (2000) pmid: 11051241
194. Fenton TR, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22891331
195. Ngeow J, et al. J. Clin. Endocrinol. Metab. (2012) pmid: 23066114
196. Lobo GP, et al. Hum. Mol. Genet. (2009) pmid: 19457929
197. Liu J, et al. Oncogene (2014) pmid: 23995781
198. Maehama T, et al. Annu. Rev. Biochem. (2001) pmid: 11395408
199. De Vivo I, et al. J. Med. Genet. (2000) pmid: 10807691
200. Ramaswamy S, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10051603
201. Liu JL, et al. Mol. Cell. Biol. (2005) pmid: 15988030
202. Karoui M, et al. Br. J. Cancer (2004) pmid: 15026806
203. Gil A, et al. PLoS ONE (2015) pmid: 25875300
204. Furnari FB, et al. Cancer Res. (1998) pmid: 9823298
205. Spinelli L, et al. J. Med. Genet. (2015) pmid: 25527629
206. Mingo J, et al. Eur. J. Hum. Genet. (2018) pmid: 29706633
207. Wang Q, et al. J. Mol. Graph. Model. (2010) pmid: 20538496
208. Andrés-Pons A, et al. Cancer Res. (2007) pmid: 17942903
209. Butler MG, et al. J. Med. Genet. (2005) pmid: 15805158
210. Georgescu MM, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10468583
211. Staal FJ, et al. Br. J. Cancer (2002) pmid: 12085208
212. Nguyen HN, et al. Oncogene (2014) pmid: 24292679
213. Rahdar M, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19114656
214. Das S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12808147
215. Wang X, et al. Biochem. J. (2008) pmid: 18498243
216. Valiente M, et al. J. Biol. Chem. (2005) pmid: 15951562
217. Nguyen HN, et al. Oncogene (2015) pmid: 25263454
218. Shan L, et al. Cell Discov (2020) pmid: 32704382
219. Blumenthal GM, et al. Eur. J. Hum. Genet. (2008) pmid: 18781191
220. Orloff MS, et al. Oncogene (2008) pmid: 18794875
221. Zbuk KM, et al. Nat. Rev. Cancer (2007) pmid: 17167516
222. Elvin JA, et al. Oncologist (2017) pmid: 28283584
223. Gao J, et al. Curr Oncol (2015) pmid: 26715889
224. Gopalan et al., 2014; ASCO Abstract 8077
225. Peguero et al., 2016; ASCO Abstract 2528
226. Konecny et al., 2016; ASCO Abstract 5557
227. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
228. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
229. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
230. Johnson DB, et al. Oncologist (2014) pmid: 24797823
231. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
232. Gamble LD, et al. Oncogene (2012) pmid: 21725357
233. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
234. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
235. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
236. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
237. Doxtader EE, et al. Hum. Pathol. (2012) pmid: 21840041
238. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
239. Kratzke RA, et al. Cancer Res. (1996) pmid: 8758904
240. Lee JU, et al. Tuberc Respir Dis (Seoul) (2012) pmid: 23101020
241. Cortot AB, et al. Clin Lung Cancer (2014) pmid: 24169260
242. Mounawar M, et al. Cancer Res. (2007) pmid: 17575133
243. Kawabuchi B, et al. Int. J. Cancer (1999) pmid: 9988232
244. Xing XB, et al. PLoS ONE (2013) pmid: 23805242
245. Lou-Qian Z, et al. PLoS ONE (2013) pmid: 23372805
246. Quelle DE, et al. Cell (1995) pmid: 8521522
247. Mutat. Res. (2005) pmid: 15878778
248. Oncogene (1999) pmid: 10498883
249. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
250. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
251. Ruas M, et al. Oncogene (1999) pmid: 10498896
252. Jones R, et al. Cancer Res. (2007) pmid: 17909018
253. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
254. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
255. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
256. Gombart AF, et al. Leukemia (1997) pmid: 9324288
257. Yang R, et al. Cancer Res. (1995) pmid: 7780957
258. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
259. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
260. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
261. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
262. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
263. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
264. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
265. Koh J, et al. Nature (1995) pmid: 7777061
266. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
267. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
268. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
269. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
270. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
271. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
272. Rutter JL, et al. Oncogene (2003) pmid: 12853981
273. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
274. Adv Exp Med Biol (2010) pmid: 20687502
275. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
276. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
277. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
278. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
279. Kaufman DK, et al. Neurology (1993) pmid: 8414022
280. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
281. Chan AK, et al. Clin Neuropathol () pmid: 28699883
282. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
283. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
284. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
285. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
286. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
287. Xu L, et al. Mol. Med. (2001) pmid: 11713371
288. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
289. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
290. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
291. Hajdenberg et al., 2012; ASCO Abstract e15010
292. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
293. Moore et al., 2019; ASCO Abstract 5513
294. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
295. Oza et al., 2015; ASCO Abstract 5506
296. Lee J, et al. Cancer Discov (2019) pmid: 31315834
297. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
298. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
299. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
300. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
301. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
302. Gourley et al., 2016; ASCO Abstract 5571
303. Kwok M, et al. Blood (2016) pmid: 26563132
304. Boudny M, et al. Haematologica (2019) pmid: 30975914
305. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
306. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
307. Mogi A, et al. J. Biomed. Biotechnol. (2011) pmid: 21331359
308. Tekpli X, et al. Int. J. Cancer (2013) pmid: 23011884
309. Vignot S, et al. J. Clin. Oncol. (2013) pmid: 23630207
310. Maeng CH, et al. Anticancer Res. (2013) pmid: 24222160
311. Itakura M, et al. Br. J. Cancer (2013) pmid: 23922113
312. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028

313. Dong ZY, et al. Clin. Cancer Res. (2017) pmid: 28039262
314. Seo JS, et al. Genome Res. (2012) pmid: 22975805
315. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
316. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
317. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
318. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
319. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
320. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
321. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
322. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
323. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
324. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
325. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
326. Lalloo F, et al. Lancet (2003) pmid: 12672316
327. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
328. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
329. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
330. Xie M, et al. Nat. Med. (2014) pmid: 25326804
331. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
332. Severson EA, et al. Blood (2018) pmid: 29678827
333. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
334. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
335. Chabon JJ, et al. Nature (2020) pmid: 32269342
336. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
337. Wu YL, et al. Lancet Oncol. (2014) pmid: 24439929
338. Passaro et al., 2019; ELCC Abstract 115O
339. Audet et al., 2013; ASCO Abstract 6041
340. Lau SC, et al. Clin Lung Cancer (2019) pmid: 31178389
341. Paz-Ares L, et al. Ann. Oncol. (2017) pmid: 28426106
342. Thongprasert S, et al. Lung Cancer Manag (2019) pmid: 31807143
343. Januszewski et al., 2018; IASLC WCLC Abstract P1.13-17
344. Suzuki et al., 2018; IASLC WCLC Abstract P1.01-92
345. Chang et al., 2018; IASLC WCLC Abstract P1.01-11
346. Llinás-Quintero N, et al. Case Rep Oncol Med (2019) pmid: 31637072
347. Miller VA, et al. Lancet Oncol. (2012) pmid: 22452896
348. Chen X, et al. Lung Cancer (2013) pmid: 23664448
349. Katakami N, et al. J. Clin. Oncol. (2013) pmid: 23816963
350. Landi L, et al. Clin Lung Cancer (2014) pmid: 25242668
351. De Grève J, et al. Lung Cancer (2015) pmid: 25682316
352. Yang JC, et al. Lancet Oncol. (2015) pmid: 26051236
353. Horn L, et al. Lung Cancer (2017) pmid: 29110849
354. Yamamoto N, et al. Adv Ther (2020) pmid: 31863283
355. Soria JC, et al. Lancet Oncol. (2015) pmid: 26156651
356. Dziadziuszko R, et al. J Thorac Oncol (2019) pmid: 30825613
357. Lai WV, et al. Eur. J. Cancer (2019) pmid: 30685684
358. Greulich H, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22908275
359. Gow CH, et al. J Thorac Oncol (2015) pmid: 26134234
360. Mazières J, et al. Ann. Oncol. (2016) pmid: 26598547
361. Mazières J, et al. J. Clin. Oncol. (2013) pmid: 23610105
362. De Grève J, et al. Lung Cancer (2012) pmid: 22325357
363. Li BT, et al. Lung Cancer (2015) pmid: 26559459
364. Costa DB, et al. J Thorac Oncol (2016) pmid: 26964772
365. Yuan B, et al. Front Oncol (2020) pmid: 32477948
366. Fang W, et al. Oncologist (2019) pmid: 31748336
367. Schuler M, et al. Ann. Oncol. (2016) pmid: 26646759
368. Wu YL, et al. Lancet Oncol. (2017) pmid: 28958502
369. Opsomer RJ, et al. Acta Urol Belg (1985) pmid: 2986437
370. Wu et al., 2018; WCLC abstract MA26.11
371. Ramalingam SS, et al. Ann. Oncol. (2016) pmid: 26768165
372. Yu HA, et al. Lung Cancer (2017) pmid: 29191595
373. Reckamp KL, et al. Cancer (2014) pmid: 24501009
374. Jänne PA, et al. Clin. Cancer Res. (2011) pmid: 21220471
375. van Geel RMJM, et al. Br. J. Cancer (2020) pmid: 32147669
376. Jänne PA, et al. J Thorac Oncol (2016) pmid: 26899759
377. Cappuzzo F, et al. Lancet Oncol. (2010) pmid: 20493771
378. Zhong WZ, et al. J. Clin. Oncol. (2019) pmid: 31194613
379. Petrelli F, et al. Clin Lung Cancer (2012) pmid: 22056888
380. Leon et al., 2014; doi.org/10.1093/annonc/mdu349.52
381. Lee CK, et al. J. Natl. Cancer Inst. (2017) pmid: 28376144
382. Yang JJ, et al. Br. J. Cancer (2017) pmid: 28103612
383. Zhou Q, et al. Cancer Cell (2021) pmid: 34388377
384. Kawashima Y, et al. Lancet Respir Med (2022) pmid: 34454653
385. Saito H, et al. Lancet Oncol (2019) pmid: 30975627
386. Piccirillo et al., 2021; ESMO Abstract 12070
387. Faehling M, et al. J Cancer Res Clin Oncol (2018) pmid: 29687154
388. Nakagawa K, et al. Lancet Oncol. (2019) pmid: 31591063
389. Han JY, et al. J. Clin. Oncol. (2012) pmid: 22370314
390. Maemondo M, et al. N. Engl. J. Med. (2010) pmid: 20573926
391. Mitsudomi T, et al. Lancet Oncol. (2010) pmid: 20022809
392. Mok TS, et al. N. Engl. J. Med. (2009) pmid: 19692680
393. Qi WX, et al. Curr Med Res Opin (2015) pmid: 25329826
394. Zhao H, et al. J Thorac Oncol (2015) pmid: 25546556
395. Wang J, et al. Int. J. Cancer (2019) pmid: 30255937
396. Baik CS, et al. J Thorac Oncol (2015) pmid: 26398831
397. Yoshioka H, et al. Ann. Oncol. (2019) pmid: 31553438
398. Fukuoka M, et al. J. Clin. Oncol. (2011) pmid: 21670455
399. Sutiman N, et al. J Thorac Oncol (2017) pmid: 27908825
400. Noronha V, et al. J. Clin. Oncol. (2019) pmid: 31411950
401. Hosomi Y, et al. J. Clin. Oncol. (2020) pmid: 31682542
402. Creelan BC, et al. Br J Cancer (2021) pmid: 33012782
403. Soria JC, et al. N. Engl. J. Med. (2018) pmid: 29151359
404. Alanazi A, et al. Lung Cancer Manag (2020) pmid: 33318755
405. Kim et al., 2021; DOI: 10.1200/PO.20.00296
406. Ramalingam SS, et al. N. Engl. J. Med. (2019) pmid: 31751012
407. Herbst et al., 2020; ASCO Abstract LBA5
408. Kenmotsu et al., 2021; ESMO Abstract LBA44
409. Soo et al., 2021; ESMO Abstract VP3-2021
410. Oxnard GR, et al. Ann. Oncol. (2020) pmid: 32139298