FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma
COUNTRY CODE
BR

REPORT DATE

ORDERED TEST #

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

PATIENT
DISEASE Lung adenocarcinoma
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings

Blood Tumor Mutational Burden - 8 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

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

EGFR T790M
KEAP1 G477V
ASXL1 E635fs*15
DNMT3A Q248*, splice site 2173+1G>A
RAD21 K605fs*7
TP53 R209fs*6

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Osimertinib** (p. 12)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 16)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***ASXL1*** **E635fs*15** (p. 9), ***DNMT3A*** **Q248*, splice site 2173+1G>A** (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 8 Muts/Mb	**No therapies or clinical trials. See Biomarker Findings section**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
Tumor Fraction - Elevated Tumor Fraction Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).**

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GENOMIC FINDINGS	VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
EGFR - T790M	0.12%	Osimertinib 1	None
		Afatinib (?)	
		Dacomitinib (?)	
		Erlotinib (?)	
		Gefitinib (?)	
10 Trials see p. 16			
KEAP1 - G477V	0.49%	None	None
1 Trial see p. 18			

(?) *Limited evidence showing variant(s) in this sample may confer resistance to this therapy*

1 *NCCN category*

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

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

ASXL1 - E635fs*15 ..... p. 9 ***DNMT3A*** - Q248*, splice site 2173+1G>A ..... p. 9

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

ASXL1 - E635fs*15 ..... p. 9
DNMT3A - Q248*, splice site 2173+1G>A ..... p. 9
RAD21 - K605fs*7 ..... p. 10
TP53 - R209fs*6 ..... p. 11

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved by the US FDA or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC, ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MEN1, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, PALB2, PMS2, POLE, PTEN, RAD51C, RAD51D, RB1, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TGFBR2, TP53, TSC1, TSC2, VHL,* and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

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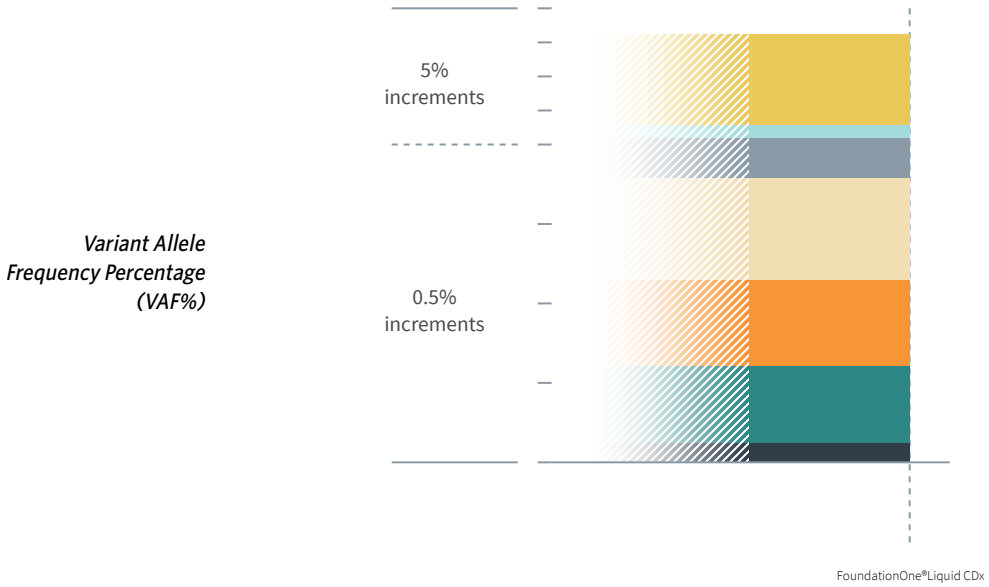

FoundationOne®Liquid CDx

HISTORIC PATIENT FINDINGS		VAF%
Blood Tumor Mutational Burden		8 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
EGFR	● T790M	0.12%
KEAP1	● G477V	0.49%
ASXL1	● E635fs*15	13.3%
DNMT3A	● Q248*	1.9%
	● splice site 2173+1G>A	1.3%
RAD21	● K605fs*7	0.54%
TP53	● R209fs*6	0.64%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx 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

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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

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BIOMARKER

Blood Tumor Mutational Burden

RESULT
8 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased blood tumor mutational burden (bTMB) may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1[3-4], anti-PD-1/CTLA4 therapies[5-6] , anti-PD-L1/CTLA4 therapies[7-10]. A Phase 2 multi-solid-tumor trial showed that bTMB ≥16 Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor[5]. In non-small cell lung cancer (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 Muts/Mb-16 Muts/Mb[1,8-10]. In head and neck squamous cell carcinoma (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[11]. In colorectal cancer (CRC), a Phase 2 study showed that bTMB TMB ≥28 Muts/Mb (approximate equivalency ≥14 Muts/Mb as measured by this assay) was associated with improved OS from a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[7].

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)[4]. 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[12]. 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[13]. 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[14]. 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)[15]. 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[16]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[16-17].

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[18-19] and cigarette smoke in lung cancer[20-21], treatment with temozolomide-based chemotherapy in glioma[22-23], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[24-28], and microsatellite instability (MSI)[24,27-28]. 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[1-2,4]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

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BIOMARKER

Tumor Fraction

RESULT
Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[29-34].

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)[35]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[36], Ewing sarcoma and osteosarcoma[37], prostate cancer[32], breast cancer[38], leiomyosarcoma[39], esophageal cancer[40], colorectal cancer[41], and gastrointestinal cancer[42].

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[43], 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[44-45].

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GENE
EGFR

ALTERATION
T790M

TRANSCRIPT ID
NM_005228.3

CODING SEQUENCE EFFECT
2369C>T

VARIANT CHROMOSOMAL POSITION
chr7:55249071

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer (NSCLC), EGFR activating mutations may predict sensitivity to EGFR–TKIs, including erlotinib[46], gefitinib[47-50], afatinib[51-54], dacomitinib[55], and osimertinib[52,56]; however, the data for patients with other tumor types are limited[57-62]. Fourth-generation EGFR inhibitors have demonstrated clinical benefit for patients with T790M and C797S-mutated non-small cell lung cancer (NSCLC)[63-64] , including a PR for a patient with L858R, T790M, and C797S mutations treated with BLU-945[63]. The efficacy of third-generation EGFR inhibitors that selectively target EGFR T790M in non-small cell lung cancer (NSCLC) has been confirmed in osimertinib[56,65-68], D-0316[69], abivertinib[70-71], alflutinib[72], naquotinib[73-76], nazartinib[77], and olmutinib[78-79]. A Phase 1 study of amivantamab monotherapy or amivantamab in combination with lazertinib for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) has produced encouraging preliminary results for treatment-naive patients and patients who relapsed after treatment with osimertinib with and without chemotherapy, including osimertinib-relapsed patients with biomarkers indicating EGFR/MET-based osimertinib resistance[80-82]. For patients with EGFR exon 18-mutated pretreated NSCLC, the updated results from the SUMMIT basket trial of neratinib reported an ORR of 34% (10/29) and median PFS of 5.8 months, including ORRs of 30% (7/23) for TKI-pretreated patients, 50% (3/6) for TKI-naive patients, and 29% (2/7) for those with brain metastases[83]. 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[84]. 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[85-86]. 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[87]. 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[88]. OR was observed in a numerically higher proportion of patients with the EGFR T790M mutation than those without this mutation[88]. The presence of a TP53 mutation, as seen here, independently associated with significantly shorter median PFS (9 vs. 14 months) and OS (16 vs. 24 months) for patients with T790M-positive metastatic NSCLC treated with second-line osimertinib[89].

— Potential Resistance —

The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, confers clinical resistance to gefitinib[90-93], erlotinib[90-91,93], afatinib[94-97], and dacomitinib[93,98-100]. Preclinical resistance to lapatinib has also been reported[101-102].

— Nontargeted Approaches —

Patients with EGFR-mutated non-squamous metastatic non-small cell lung cancer (NSCLC) who progressed on EGFR TKI have benefited from immune checkpoint inhibitors combined with antiangiogenic therapy and chemotherapy, particularly atezolizumab plus bevacizumab plus carboplatin and paclitaxel (OS HR=0.61 compared with bevacizumab/chemotherapy)[103-105] or sintilimab plus bevacizumab biosimilar IBI305 plus cisplatin and pemetrexed (PFS HR=0.46 compared with chemotherapy alone)[106].

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[107-109] and in 4% of lung squamous cell carcinomas[110]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[111-116]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[117-118]. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[119-120]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[121] or resected Stage 1 NSCLC[122]. In a retrospective study of lung adenocarcinoma treated with surgical resection without neoadjuvant TKIs, significantly shorter OS and recurrence-free survival was observed for patients harboring uncommon EGFR mutations (G719X, T790M, or L861R/Q) compared with those harboring only common mutations (L858R or exon 19 deletion)[123].

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[124]. The EGFR T790M mutation, when co-occurring with EGFR activating alterations, has been associated with clinical resistance to gefitinib[90-93], erlotinib[90-91,93], dacomitinib[93,98-100], and afatinib[94-97,125], as well as preclinical resistance to lapatinib[101-102]. Rare cases of EGFR T790M without a concurrent activating alteration have been reported[126] and germline T790M mutations have been reported to predispose to familial lung adenocarcinoma[126-128]. Limited preclinical data suggests T790M alone is weakly activating, and increased EGFR activity is observed when T790M is expressed with certain activating EGFR alterations[129]. Therefore, although this alteration has not been fully characterized, it is likely to result in reduced sensitivity to first- and second-generation EGFR inhibitors.

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GENE
KEAP1

ALTERATION
G477V

TRANSCRIPT ID
NM_012289.3

CODING SEQUENCE EFFECT
1430G>T

VARIANT CHROMOSOMAL POSITION
chr19:10600425

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A study of patients with localized non-small cell lung cancer (NSCLC) identified pathogenic KEAP1 and NFE2L2 mutations as predictors of local recurrence following radiotherapy but not surgery; limited preclinical data also showed that treatment with a glutaminase inhibitor sensitized KEAP1-mutated NSCLC cells to radiation[130]. In other preclinical studies, treatment with AKT inhibitors sensitized lung cancer cells harboring KEAP1 or NFE2L2 mutations to both chemotherapy and radiation therapy[131-132]. Mixed clinical data have been reported for the association between KEAP1 mutations and the response to immunotherapy. A pan-cancer study of immunotherapy showed that patients with KEAP1 mutations had shorter OS (10 vs. 20 months) than those without[133]. However, another study across solid tumors showed that KEAP1 mutations were associated with higher tumor mutational burden (TMB) and PD-L1 expression, as well as improved survival outcomes with immunotherapy compared with other treatments (20.0 vs. 11.5 months)[134]. For patients with non-small cell lung cancer (NSCLC), a study of PD-L1 inhibitors showed that patients with concurrent mutations of STK11 and KEAP1 (n=39) experienced significantly shorter PFS (1.6 vs. 2.5 months, HR=1.5) and OS (4 vs. 11 months, HR=1.9) compared with patients with STK11- and KEAP1-wildtype tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 Muts/Mb)[135]. Retrospective analyses of patients with NSCLC who received immunotherapy reported reduced OS (p=0.040) for patients harboring KEAP1- or NFE2L2-mutated tumors[136] or STK11- or KEAP1-mutated tumors (p <0.001)[137] compared with those without. Studies of immune checkpoint inhibitors for patients with lung adenocarcinoma showed that coexisting mutations between KEAP1, PBRM1, SMARCA4, STK11, and KRAS were associated with worse OS[138]. An exploratory analysis of a subset of patients with PD-L1-positive NSCLC treated in the first-line setting with pembrolizumab showed similar ORR, PFS, and OS when comparing patients with STK11 or KEAP1 mutations and those without[139]. In addition, preclinical data suggest that KEAP1 inactivation increases tumor demand for glutamine and increases tumor sensitivity to glutaminase inhibitors like telaglenastat[140-142]. Limited clinical data suggest that KEAP1 mutations may predict improved clinical benefit from combinations of glutaminase inhibitors and anti-PD-1 inhibitors[143]; a Phase 1/2 study of the glutaminase inhibitor telaglenastat (CB-839) plus nivolumab to treat advanced NSCLC reported better clinical benefit rates and median PFS for patients with KEAP1 mutations (75% [3/4] vs. 15% [2/13], 6.4 vs. 3.7 months), KRAS mutations (38% [3/8] vs. 20% [2/10], 4.5 vs. 3.7 months), or KEAP1 and KRAS concurrent mutations (100% [2/2] vs. 13% [1/8], 7.2 vs. 3.7 months) compared with patients without these mutations[143]. The KEAP1 mutation has also been identified as a potential biomarker for sensitivity to combined AKT and TXNRD1 inhibition in lung cancer[144].

FREQUENCY & PROGNOSIS

Somatic mutation of KEAP1 occurs in a range of solid tumors, including gastric, hepatocellular, colorectal, and lung cancers[145]. KEAP1 mutations are rare in hematological malignancies, occurring in fewer than 1% of samples analyzed (COSMIC, 2022)[146]. In a retrospective analysis of the pan-solid MSKCC dataset, KEAP1 mutation correlated with reduced OS (13.28 vs. 26.53 months)[134]. For patients with non-small cell lung cancer (NSCLC), mutation of KEAP1 and/or NFE2L2 also correlated with reduced median OS (11.51 vs. 22.32 months)[134]. In another study, for NSCLC treated with frontline chemotherapy, multivariate analysis showed that KEAP1 and/or NFE2L2 mutations significantly associated with reduced survival for patients with adenocarcinoma (PFS HR=2.34, OS HR=1.96) but not for patients with squamous cell carcinoma[147].

FINDING SUMMARY

KEAP1 encodes a substrate adaptor protein that regulates the cellular response to oxidative stress by providing substrate specificity for a CUL3-dependent ubiquitin ligase[148]. KEAP1 exerts anti-tumor effects through negative regulation of NRF2, a transcription factor encoded by NFE2L2[149-151]; KEAP1 inactivation promotes cancer progression through NRF2-mediated chemoresistance and cell growth[150-151].

GENE
ASXL1

ALTERATION
E635fs*15

TRANSCRIPT ID
NM_015338.5

CODING SEQUENCE EFFECT
1900_1922del23

VARIANT CHROMOSOMAL POSITION
chr20:31022402-31022425

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in ASXL1.

FREQUENCY & PROGNOSIS

ASXL1 alterations occur infrequently across various solid tumor types[152] and are not known to act as drivers in any specific solid cancer type[153]. Published data investigating the prognostic implications of ASXL1 alterations in solid tumors are limited (PubMed, May 2022). In the context of clonal hematopoiesis, ASXL1 mutations are significantly enriched in current or former smokers[154].

FINDING SUMMARY

ASXL1 regulates epigenetic marks and transcription through interaction with polycomb complex proteins and various transcription activators and repressors[155-157]. Alterations such as seen here may disrupt ASXL1 function or expression[158-160].

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[161-166]. 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[161-162]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[167]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[165,168-169]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
DNMT3A

ALTERATION
Q248*, splice site 2173+1G>A

TRANSCRIPT ID
NM_022552.3, NM_022552.3

CODING SEQUENCE EFFECT
742C>T, 2173+1G>A

VARIANT CHROMOSOMAL POSITION
chr2:25471019, chr2:25463508

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2022)[170-171]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2022).

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[172-173]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[174-179]. Alterations such as seen here may disrupt DNMT3A function or expression[180-183].

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[161-166]. 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[161-162]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[167]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[165,168-169]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
RAD21

ALTERATION
K605fs*7

TRANSCRIPT ID
NM_006265.2

CODING SEQUENCE EFFECT
1814delA

VARIANT CHROMOSOMAL POSITION
chr8:117859820-117859821

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to target alterations in this gene.

FREQUENCY & PROGNOSIS

RAD21 amplifications have been reported in solid tumors, including breast cancers (7%), melanoma (5.4%), and prostate (2.4%) cancers[152]. RAD21 overexpression has been correlated with poor prognosis in endometrial cancer[184], breast cancer[185-186], Ewing sarcoma[187], and colorectal cancer (CRC), especially in KRAS-mutant CRC[188].

FINDING SUMMARY

RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[189-192]. In preclinical studies, downregulation of RAD21 or other cohesin components leads to loss of expression from amplified genes, as well as amplifications themselves upon cell passaging[193], but also leads to an increase in deletions, insertions, and other rearrangements[194]. High RAD21 expression has also been associated with increased genomic instability[195]. Cohesin complex also organizes chromatin domains and regulates gene expression[196-197]. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression[198]. RAD21 amplification has been correlated with increased expression in breast[185,195,199] and endometrial[184] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

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GENE
TP53

ALTERATION
R209fs*6

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
626_627delGA

VARIANT CHROMOSOMAL POSITION
chr17:7578221-7578223

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[200-203] or p53 gene therapy such as SGT53[204-208]. 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[209]. 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[210]. 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[211]. 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[212]. 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[213]. 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[214]. 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[215]. 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[208]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[216]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[217]. The presence of a TP53 mutation, as seen here, independently associated with significantly shorter median PFS (9 vs. 14 months) and OS (16 vs. 24 months) for patients with T790M-positive metastatic NSCLC treated with second-line osimertinib[89].

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)[109-110,218-223], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2022)[108-110,224]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2022)[170-171]. 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[225]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[226].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[227]. Alterations such as seen here may disrupt TP53 function or expression[228-232].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[233]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[234-236], including sarcomas[237-238]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[239] to 1:20,000[238]. 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[240]. 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[161-166]. 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[161-162]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[167]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[165,168-169]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Osimertinib

Assay findings association

EGFR
T790M

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR TKI-sensitizing mutations or rearrangements and/or the EGFR T790M mutation may predict sensitivity to osimertinib in non-small cell lung cancer[56,68,241-243] .

SUPPORTING DATA

In a Phase 3 study for patients with EGFR T790M-positive advanced NSCLC who progressed on EGFR TKI therapy, osimertinib compared with combination platinum therapy led to longer median PFS (10.1 months vs. 4.4 months), including for patients with central nervous system metastases (8.5 vs. 4.2 months). An ORR of 71% was achieved with osimertinib compared to 31% with combination platinum therapy[244]. The efficacy of osimertinib is confirmed by earlier phase studies in this setting[56,65-67] , and in a real-world setting for patients with T790M-positive advanced NSCLC pretreated with EGFR TKIs[245-246] . Case studies report that 2 patients with T790M-mutated NSCLC achieved durable PRs to osimertinib rechallenge after the adverse events induced by initial osimertinib treatment had been resolved[247-248] . 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)[249]. 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)[250]. 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[251].

Afatinib

Resistance of variant(s) to associated therapy is unclear

Assay findings association

EGFR
T790M

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[51,55,252-253] , whereas data for patients with other tumor types are limited[57-62,254] . EGFR T790M, in the presence of a co-occurring activating EGFR alteration, has been associated with clinical resistance to afatinib and has been reported in 33-48% of patients who progressed on the inhibitor across multiple studies[94-97,125] . Although DCRs of more than 50% have been reported for patients with erlotinib- or gefitinib-resistant NSCLC treated with afatinib[255], including T790M-positive patients[256], 1 study observed that overall survival for patients with T790M-positive NSCLC was worse than for patients who were T790M-negative (HR=1.79, p=0.005)[257].

SUPPORTING DATA

Afatinib enabled a DCR of 64.3% (9/14) for patients with advanced T790M-positive NSCLC in a post-hoc analysis of Phase 2 and Phase 3 trials[256]. For T790M-positive patients who were TKI-naive or -pretreated, afatinib treatment resulted in ORRs of 24.0% (6/25) and 18.8% (12/64), respectively, in a large-scale retrospective analysis of EGFR-mutated NSCLC[258]. Another large-scale retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 21.1% (4/19) for T790M-positive patients and an ORR of 24.4% (105/431) for the entire cohort[259]. For heavily pre-treated patients with erlotinib- or gefitinib-resistant NSCLC and T790M-positivity, the combination of afatinib with cetuximab enabled an ORR of 31.7% (40/126) in a Phase 1b study[260], and 1/1 PR in a case series[261]. A patient with T790M-positive NSCLC who progressed on erlotinib experienced a PR to afatinib combined with panitumumab in another case series[262]. 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%[255-256,263-266] ; however, DCRs of more than 50% have been observed[255]. 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[267] or osimertinib[268], respectively. In the LUX-Lung 1 Phase 2b/3 trial for patients with advanced non-small cell lung cancer (NSCLC) who previously progressed on first-generation EGFR tyrosine kinase inhibitors, afatinib treatment resulted in longer median PFS (mPFS; 3.3 vs. 1.1 months, HR=0.38) but no significant difference in median OS (mOS; 10.8 vs. 12.0 months, HR=1.08) when compared with placebo[263]; similar results were observed in the single-arm LUX-Lung 4 trial in the same treatment setting[265]. The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer mOS (7.9 vs. 6.8 months, HR=0.81), significantly longer mPFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[269]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[270].

Dacomitinib

Resistance of variant(s) to associated therapy is unclear

Assay findings association

EGFR
T790M

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[51,55,252-253] , whereas data for patients with other tumor types are limited[57-62,254] . EGFR T790M, in the presence of a co-occurring activating EGFR alteration, is associated with clinical resistance to dacomitinib[93,98-99,271-272] .

SUPPORTING DATA

A randomized Phase 3 trial for patients with non-small cell lung cancer (NSCLC) harboring activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS [mOS] of 34.1 vs. 26.8 months, HR=0.760; median PFS [mPFS] of 14.7 vs. 9.2 months, HR=0.59)[273-274] ; mOS was 34.1 to 36.7 months and ORR was 75% to 79%, depending on the dosing regimen[275]. A pooled subgroup analysis for patients with NSCLC harboring activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (mPFS of 14.6 vs. 9.6 months, HR=0.717; mOS of 26.6 vs. 23.2 months, HR=0.737)[276]. An analysis of dacomitinib in NSCLC comparing common activating EGFR alterations alone with co-occurring common and uncommon EGFR mutations showed no statistically significant difference in total ORR (33% vs. 40%, p=0.636) or DCR (77% vs. 73%, p=0.089); however, multivariate analysis revealed compound mutation status as an independent predictor of worse OS (HR=5.405)[277]. 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[278]. Phase 1/2 studies of dacomitinib for patients with advanced KRAS-wildtype non-small cell lung cancer (NSCLC) who had previously progressed on chemotherapy and erlotinib or gefitinib and were not selected for EGFR mutations reported ORRs of 4.6-17% (3/66-9/53), median PFS of 3-4 months, and median OS of 9-11 months[93,279] .

Erlotinib

Resistance of variant(s) to associated therapy is unclear

Assay findings association

EGFR
T790M

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[46,280-282] . The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, has been associated with resistance to erlotinib and gefitinib[90-93] .

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)[46,283] . This study and meta-analyses attribute the lack of OS benefit to the effectiveness of post-progression salvage therapy in the control arm[284]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[285]. 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)[286], the NEJ026 trial for Japanese patients (16.9 vs. 13.3 months, HR=0.605)[287-288] , and the international BEVERLY trial (15.4 vs. 9.7 months, HR=0.60)[289]; 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[280,290] . 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[281]. 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)[291].

Gefitinib

Resistance of variant(s) to associated therapy is unclear

Assay findings association

EGFR
T790M

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[282,292-297] , and responses have been reported for patients with EGFR-rearranged NSCLC[243,298] . The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, has been associated with resistance to erlotinib and gefitinib[90-93] .

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[47]. Phase 3 studies for Japanese patients[294,299] and East Asian patients[295,300] 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)[301]. 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[302-303] . 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[304].

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

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
EGFR

ALTERATION
T790M

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies. In the context of co-occurring activating alterations, EGFR T790M confers clinical resistance to erlotinib, gefitinib, afatinib, lapatinib, and dacomitinib. Other agents may be relevant, including irreversible EGFR inhibitors, and in the context of lung cancer, the ALK/EGFR/ROS1 inhibitor brigatinib.

NCT05559645

PHASE NULL

Assessing an Oral EGFR Inhibitor, DZD9008 in Patients With Advanced Non-small Cell Lung Cancer(NSCLC) With EGFR Mutations (WU-KONG15)

TARGETS
ERBB2, EGFR

LOCATIONS: Beijing (China)

NCT04765059

PHASE 3

A Study to Evaluate Chemotherapy Plus Osimertinib Against Chemotherapy Plus Placebo in Patients With Non-small Cell Lung Cancer (NSCLC)

TARGETS
EGFR

LOCATIONS: Maryland, Massachusetts, Sevilla (Spain), Madrid (Spain), Alicante (Spain), León (Spain), Valencia (Spain), Oviedo (Spain), Palma de Mallorca (Spain), Minnesota

NCT05020769

PHASE 2/3

SI-B001 Combined With Osimertinib Mesylate Tablets in the Treatment of Recurrent Metastatic Non-small Cell Lung Cancer.

TARGETS
EGFR, ERBB3

LOCATIONS: Guangdong (China)

NCT04140526

PHASE 1/2

Safety, PK and Efficacy of ONC-392 in Monotherapy and in Combination of Anti-PD-1 in Advanced Solid Tumors and NSCLC

TARGETS
PD-1, CTLA-4, EGFR

LOCATIONS: Florida, Georgia, South Carolina, Tennessee, District of Columbia, Virginia

NCT04486833

PHASE 1/2

TUSC2-nanoparticles (GPX-001) and Osimertinib in Patients With Stage IV Lung Cancer Who Progressed on Osimertinib Alone

TARGETS
EGFR

LOCATIONS: Virginia, Maryland, Texas, Colorado, California

NCT04349267

PHASE 1/2

Study of BMS-986315 Alone and in Combination With Nivolumab or Cetuximab in Participants With Advanced Solid Tumors

TARGETS
NKG2A, PD-1, EGFR

LOCATIONS: Tennessee, Montreal (Canada), Toronto (Canada), Ottawa (Canada), South Dakota, Edmonton (Canada), Vancouver (Canada)

NCT05089916

PHASE 2

Radiation During Osimertinib Treatment: a Safety and Efficacy Cohort Study

TARGETS
EGFR

LOCATIONS: München (Germany)

NCT03497767

PHASE 2

A Randomised Phase II Trial of Osimertinib With or Without SRS for EGFR Mutated NSCLC With Brain Metastases

TARGETS
EGFR

LOCATIONS: Melbourne (Australia), Sydney (Australia), Newcastle (Australia), Brisbane (Australia), Singapore (Singapore)

NCT05215951

PHASE 2

Osimertinib Plus Chemotherapy in Uncommon EGFRm NSCLC.

TARGETS
EGFR

LOCATIONS: Chengdu (China), Nan Chong (China), Harbin (China)

NCT05104281

PHASE 3

Osimertinib Combined With Bevacizumab in Patients With Brain Metastasis Epidermal Growth Factor Receptor (EGFR) Mutation Positive Metastatic Non-Small Cell Lung Cancer

TARGETS
VEGFA, EGFR

LOCATIONS: Qingdao (China)

GENE
KEAP1

ALTERATION
G477V

RATIONALE
KEAP1 inactivation may predict sensitivity to glutaminase inhibitors.

NCT05039801

PHASE 1

IACS-6274 With or Without Pembrolizumab for the Treatment of Advanced Solid Tumors

TARGETS
GLS, PD-1

LOCATIONS: Texas

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

CDH1
E763A

ERBB4
W513C

FANCC
Q357E

FGF14
K66N

FGFR4
E697D

KMT2A (MLL)
E3751K

MSH3
P69_A70insPAP

NF1
R2349L

SMO
P696S

SOX9
P92A

SPEN
M3567I

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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)	***KRAS***

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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.

LTK	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*	*MAPK1*
MCL1	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***	*MITF*
MKNK1	*MLH1*	***MPL*** **Exon 10**	*MRE11* (MRE11A)	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*	*MTAP*
MTOR **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*	***NF1***
NF2	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**	***NRAS*** **Exons 2, 3**
NSD2 (WHSC1 or MMSET)	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARP1	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**	***PDGFRB*** **Exons 12-21, 23**
PDK1	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*	*POLD1*
POLE	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PRKN* (PARK2)	*PTCH1*
PTEN	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C* (FAM46C)	*TERC** ncRNA	***TERT**** **Promoter**
TET2	*TGFBR2*	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*
TYRO3	*U2AF1*	***VEGFA***	*VHL*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF THERAPIES AND CLINICAL TRIALS

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

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*,

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KMT2D (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

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

REPORT HIGHLIGHTS

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

Certain sample of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

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SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.4.0

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