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

PATIENT

DISEASE Lung adenocarcinoma
NAME Hasic, Lejla
DATE OF BIRTH 14 July 1969
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN Dijana, Kopric
MEDICAL FACILITY BA-Univerzitetsko klinički centar Tuzla
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 314741
PATHOLOGIST Provided, Not

SPECIMEN

SPECIMEN ID BA03-2020-00025048 7/14/1946
SPECIMEN TYPE Blood
DATE OF COLLECTION 15 July 2020
SPECIMEN RECEIVED 20 July 2020
SAMPLE COVERAGE 4,588x

Biomarker Findings

MSI Status Undetermined.

Genomic Findings

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

EGFR **exon 19 deletion (E746_A750del), T790M, amplification**
TP53 **V216M**

3 Therapies with Clinical Benefit
2 Therapies with Lack of Response
10 Clinical Trials

BIOMARKER FINDINGS

MSI Status Undetermined

GENOMIC FINDINGS		MAF %
EGFR -	exon 19 deletion (E746_A750del)	61.2%
	T790M	56.7%
	amplification	-

10 Trials see p. 9

ACTIONABILITY

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)	
Osimertinib	1	Cetuximab	2A
⚠ Erlotinib[1]		Panitumumab	
⚠ Gefitinib[1]			

⚠ *1. Patient may be resistant to indicated therapy*

☐ *NCCN category*

GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. In the appropriate clinical context, germline testing of *APC*, *BRCA1*, *BRCA2*, *CDH1*, *NF1*, *PALB2*, *RB1*, *RET*, *STK11*, and *TP53* is recommended.

Mutant Allele Frequency is not applicable for copy number amplifications.

Electronically signed by J. Keith Killian, M.D. | 03 August 2020
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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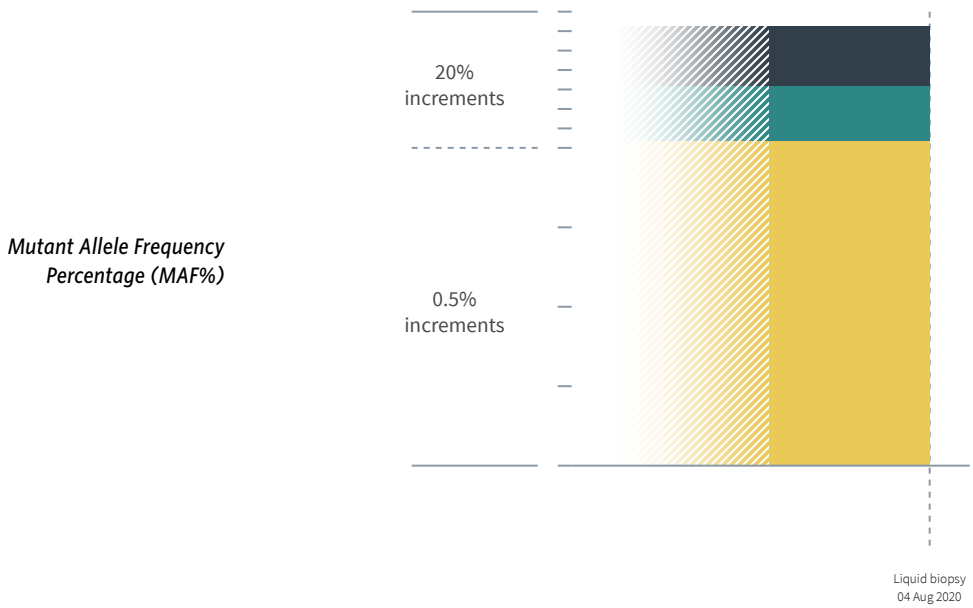
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531



HISTORIC PATIENT FINDINGS		TEST 1 MAF%
EGFR	● exon 19 deletion (E746_A750del)	61.2%
	● T790M	56.7%
	amplification	Present
TP53	● V216M	9.5%

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

GENE
EGFR

ALTERATION
exon 19 deletion (E746_A750del), T790M, amplification

TRANSCRIPT NUMBER
NM_005228

CODING SEQUENCE EFFECT
- 2236_2250delGAATTAAGAGAAGCA
- 2369C>T

POTENTIAL TREATMENT STRATEGIES

EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[1], gefitinib[2], afatinib[3], dacomitinib[4], and osimertinib[5]. However, strong clinical evidence indicates that the EGFR T790M mutation confers resistance to gefitinib and erlotinib[6], and preclinical studies indicate that cells expressing EGFR T790M are resistant to lapatinib[7-8]. T790M has also been reported in 40 to 57% of patients with acquired afatinib resistance[9], suggesting patients with T790M may be less responsive to this therapy[9-11]; however, DCRs of more than 50% have been reported for patients with erlotinib- or gefitinib-resistant NSCLC treated with afatinib[12], including T790M-positive patients[13]. Nine patients with NSCLC harboring EGFR T790M who were treated with afatinib after osimertinib failure exhibited 5 SDs and 4 PDs, with a median PFS of 2 months[14]. A combination of afatinib and cetuximab has shown clinical efficacy for T790M-positive NSCLC[15-16], although careful dosing may be required[16-17]. Brigatinib has shown preclinical efficacy against mutant EGFR, including T790M, C797S, and exon-19-deletion triple-mutated mouse models, particularly when in combination with cetuximab[18]. However, brigatinib monotherapy in EGFR-mutant NSCLC cases in the presence or absence of T790M has been associated with limited clinical efficacy (2 PRs, 14 SDs, and 26 PDs)[19]. Third-generation EGFR inhibitors, such as osimertinib, selectively target mutated EGFR, including EGFR T790M[5,20]. Osimertinib achieved an ORR of 61% in T790M-positive cases and 21% in T790M-negative cases[5]. Resistance to EGFR inhibition may arise by reactivation of the MAPK pathway, and preclinical evidence suggests that co-targeting EGFR and MAPK signaling may retard the development of acquired resistance to third-generation EGFR inhibitors[21-23]. EGFR amplification or expression may be associated with benefit from anti-EGFR antibodies, such as cetuximab[24-27], panitumumab[25], or necitumumab[28], or EGFR TKIs that target wild-type EGFR[29-33]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin[34-35] that has also shown benefit in patients with CRC and melanoma[36-37]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy[38-41]. Preclinical studies have reported that EGFR-mutant cells[38-40], including cells with exon 20 insertions[42], are sensitive to HSP90 inhibitors. For patients with EGFR exon 19 deletion/ L858R-positive and T790M- negative NSCLC who had previously progressed on first or second generation EGFR TKIs, a Phase 1 study evaluating the HER3-targeted antibody U3-1402 reported tumor reduction in 12 patients with 2 confirmed PRs (2/13)[43]. Consistent with preclinical data demonstrating that the EGFR inhibitor AZD3759 is capable of penetrating the blood-brain barrier and reducing the volume of brain and leptomeningeal metastases, preliminary results from a Phase 1 trial evaluating single-agent AZD3759 reported a reduction in the volume of brain metastases in 40.0% (8/20) of patients with previously treated NSCLC harboring either EGFR L858R or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[44-45]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54.3% (69/127) for all evaluable patients and 44.4% (8/18, intracranial) for patients with brain metastases[46]. The reovirus Reolysin targets cells with activated RAS signaling[47-49] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[50-58]. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear[59]. The Phase 3 IMpower study showed that the addition of atezolizumab to bevacizumab plus chemotherapy treatment also had clinical efficacy in patients with untreated EGFR-mutated or ALK-rearranged metastatic NSCLC[60]; therefore, the patient's clinical context should be considered.

FREQUENCY & PROGNOSIS

Amplification of EGFR has been variously reported in 4-42% of non-small cell lung carcinoma (NSCLC) samples[61-65]. EGFR mutation has been reported in 12-36% of lung adenocarcinomas[61,66-67] and in 4% of lung squamous cell carcinomas[62]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[63-65,68-70]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[71-72]. 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)[73]. In lung adenocarcinoma, EGFR gene amplification was a predictor of poor disease-free survival in all patients and of poor overall survival in patients with EGFR mutations[74-75]. Nuclear expression of EGFR in NSCLC has been reported to associate with higher disease stage, shorter progression-free survival, and shorter overall survival[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]. The EGFR mutation seen here is a deletion in exon 19, encoding a portion of the kinase domain of EGFR; such mutations have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib[80-82], afatinib[83], osimertinib[20], and dacomitinib[4,84], although limited preclinical data suggest reduced sensitivity to lapatinib[8,85]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[64,86-87]. The EGFR T790M resistance mutation suggests that this tumor may be resistant to the first-generation EGFR inhibitors gefitinib and erlotinib[6] and may be less responsive to the second-generation EGFR inhibitor afatinib[9]. The amplification of EGFR with the T790M mutation has also been linked to resistance to the irreversible EGFR inhibitor dacomitinib[88].

GENE
TP53

ALTERATION
V216M

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
646G>A

POTENTIAL TREATMENT STRATEGIES

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[89-92], or p53 gene therapy and immunotherapeutics such as SGT-53[93-97] and ALT-801[98]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[99]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[100]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[101]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[102]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[103]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[104]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[97]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[105]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[106-108]. In a Phase 1b trial in 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[109]. 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[110-111]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[112-113]. 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)[61-62,114-119], including 38-54% of lung adenocarcinomas and 47-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Sep 2019)[61-62,67,120]. 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[121]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[122].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[123]. Alterations that have been functionally characterized as inactivating and/or result in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, are thought to dysregulate the transactivation of p53-dependent genes and are predicted to promote tumorigenesis[124-128]. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[129-131], including sarcomas[132-133]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[134] to 1:20,000[133]. 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[135]. In the appropriate clinical context, germline testing of TP53 is recommended.

Osimertinib

Assay findings association

EGFR
exon 19 deletion (E746_A750del), T790M, amplification

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 as first-line treatment for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations as well as to treat patients with metastatic EGFR T790M-positive NSCLC and disease progression on or after EGFR TKI therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations and/or the EGFR T790M mutation may predict sensitivity to osimertinib[5,20,136] . T790M-positive patients showed higher response rates than T790M-negative cases in a Phase 1 study for patients with acquired EGFR TKI resistance (61% vs. 21%)[5]. 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[20].

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)[20,137] . 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)[138]. 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[5]. 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[139]. The efficacy of osimertinib is confirmed by earlier phase studies in this setting[5,140-142] , and in a real-world setting for patients with T790M-positive advanced NSCLC pretreated with EGFR TKIs[143-144] . 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[145-146] . The Phase 1b TATTON study of osimertinib in combination with selumetinib, savolitinib, or durvalumab for patients with previously treated EGFR-mutated lung cancer reported ORRs of 41.7% (15/36), 44.4% (8/18), and 43.5% (10/23), respectively[147].

Erlotinib

⚠ Patient may be resistant to Erlotinib

Assay findings association

EGFR
exon 19 deletion (E746_A750del), T790M, amplification

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. In patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[148]. A heavily pretreated patient with KRAS wild-type metastatic pancreatic ductal adenocarcinoma and an EGFR exon 19 deletion experienced a sustained partial response for 32 weeks to erlotinib monotherapy[149]. In a prospective study of advanced NSCLC treated with gefitinib (n=102), EGFR copy gain was significantly associated with improved survival (HR=0.44)[31]. Several meta-analyses spanning 14 to 20 studies of patients with advanced NSCLC receiving single-agent erlotinib or gefitinib (n=1725 to 1854) reported the association of increased EGFR copy number with improved OS (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11)[29-30,150] . The EGFR T790M mutation has been associated with resistance to erlotinib and gefitinib, leading to the suggestion that these drugs will not be effective in a tumor that contains the T790M mutation, particularly in patients who have already received erlotinib or gefitinib[6].

SUPPORTING DATA

The initial approval of erlotinib to treat patients with NSCLC was based on the Phase 3 BR.21 trial, which demonstrated prolonged OS for genomically unselected patients treated with erlotinib compared with those treated with standard chemotherapy[151]. For patients with EGFR-mutated NSCLC, the Phase 3 EURTAC trial reported improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37)[1]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[152]. Meta-analysis of studies comparing erlotinib or gefitinib versus chemotherapy in the first-line setting reported no significant improvement in OS for patients with EGFR-mutated NSCLC; however, the lack of improved OS was attributed to the effectiveness of postprogression salvage therapy[153]. In the maintenance setting, the placebo-controlled Phase 3 SATURN trial reported significantly improved PFS with maintenance erlotinib following first-line platinum-based chemotherapy irrespective of EGFR status; however, the largest effect was seen for patients with EGFR mutations (HR=0.10)[154]. 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 advanced EGFR-mutated NSCLC[155]. 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)[156]. In a Phase 2 trial, no clinical benefit was observed from the addition of bevacizumab to erlotinib for patients with NSCLC harboring EGFR exon 19 deletion or L858R mutation[157]. In one study, median PFS (4.1 vs. 11.7 months, HR=9.7) and median OS (14.1 vs. 47.0 months, HR=10.2) were significantly shorter for patients with NSCLC harboring EGFR L747_A750>P (n=6) relative to those with deletions affecting EGFR E746_A750 (n=24) treated with first-line erlotinib[158].

Gefitinib

⚠ Patient may be resistant to Gefitinib

Assay findings association

EGFR
exon 19 deletion (E746_A750del), T790M, amplification

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

Amplification or activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and progression-free survival for patients with EGFR-mutated NSCLC treated with gefitinib, compared to chemotherapy[148,159-164] . In a prospective study of advanced NSCLC treated with gefitinib (n=102), EGFR copy gain was significantly associated with improved survival (HR=0.44)[31]. Several meta-analyses spanning 14 to 20 studies of patients with advanced NSCLC receiving single-agent erlotinib or gefitinib (n=1725 to 1854) reported the association of increased EGFR copy number with improved OS (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11)[29-30,150] . Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant overall survival benefit from gefitinib compared to placebo (HR = 0.21)[165-166] . The EGFR T790M mutation has been associated with resistance to erlotinib and gefitinib, leading to the suggestion that these drugs will not be effective in a tumor that contains the T790M mutation, particularly in patients who have already received erlotinib or gefitinib[6].

SUPPORTING DATA

A Phase 3 trial of first-line gefitinib therapy for patients with NSCLC and EGFR exon 19 deletions or L858R mutations reported a longer PFS (9.2 months vs. 6.3 months)[161] but no change in median OS (34.9 months vs. 37.2 months) compared with patients treated with cisplatin plus docetaxel (median OS of 37.2 months)[167]. Gefitinib achieved an ORR of 69.8% and an OS of 19.2 months as first-line treatment for Caucasian patients with non-small cell lung carcinoma (NSCLC) and EGFR sensitizing mutations[2]. In the retrospective analysis of a Phase 3 study for East Asian patients, gefitinib was reported to have a longer PFS for patients with EGFR mutation-positive NSCLC compared with carboplatin/paclitaxel doublet chemotherapy[162,168] . Two Phase 3 trials of 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 PFSs (16 and 20.9 months vs. 8 and 11.9 months), and longer median OSs (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[169-170] . Retrospective analysis of East Asian patients with advanced NSCLC receiving first-line gefitinib therapy reported that patients with EGFR exon 19 mutations experienced a longer median PFS (10.9 months) compared with patients with EGFR mutations in exon 18 (7.9 months), exon 20 (1.2 months), exon 21 (7.7 months), or double mutations (5.7 months); however, no differences in OS were seen between EGFR mutations[171]. In a Phase 1 study for treatment-naive patients with NSCLC, best ORRs of 78% (7/9) were observed in patients treated with combination gefitinib and the PD-L1 inhibitor durvalumab as first-line treatment and of 80% (8/10) in those treated with the combination after gefitinib monotherapy[172].

Cetuximab

Assay findings association

EGFR
exon 19 deletion (E746_A750del), T790M, amplification

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Cetuximab is also approved for BRAF V600E-mutated CRC in combination with the BRAF inhibitor encorafenib. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR amplification may confer sensitivity to EGFR inhibitory antibodies such as cetuximab. For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[25].

SUPPORTING DATA

In previously untreated patients with non-small cell lung cancer (NSCLC), the FLEX study demonstrated that in NSCLC tumors with high expression of EGFR, treatment with cetuximab plus chemotherapy resulted in longer overall survival compared to chemotherapy alone; there was no clear association between cetuximab response and EGFR mutations in this trial[24]. In a Phase 2 study of 31 patients with Stage 3 NSCLC, the addition of cetuximab to radiotherapy and chemotherapy produced an overall response rate of 67%; EGFR gene copy number was not predictive of efficacy outcome[173]. A Phase 3 study of 938 patients with progressive non-small cell lung cancer after platinum-based therapy concluded that, in unselected patients, the addition of cetuximab to chemotherapy was not recommended in this second-line setting[174]. Cetuximab is also being studied as part of a therapeutic regimen for patients with EGFR mutations who develop secondary resistance to erlotinib or gefitinib. A Phase 1b study combining afatinib and the anti-EGFR antibody cetuximab in patients with advanced EGFR-mutant lung cancer with acquired resistance to erlotinib/gefitinib observed an overall objective response rate of 29%, and comparable response rates in both T790M-positive and T790M-negative tumors (32% vs. 25%)[15]. A Phase 1 study of combination erlotinib and cetuximab treatment in patients with NSCLC, including those with squamous tumors, inhibitor-resistant EGFR mutations, and wild-type EGFR, as well as those who had progressed on prior erlotinib treatment, reported partial responses in two of 20 patients and stable disease lasting at least 6 months in three of 20 patients[175]; however, in this study a patient identified with an exon 19 deletion and T790M progressed rapidly on cetuximab and erlotinib[176].

Panitumumab

Assay findings association

EGFR
exon 19 deletion (E746_A750del), T790M, amplification

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[25].

SUPPORTING DATA

In a Phase 2 trial in patients with advanced non-small cell lung cancer (NSCLC), the addition of panitumumab to paclitaxel/carboplatin did not result in improved clinical benefit[177], and subsequent studies investigating the addition of panitumumab to pemetrexed/cisplatin reported no benefit for patients with wild-type KRAS lung adenocarcinoma[178]. The combination of afatinib and panitumumab has been explored for 2 patients with EGFR T790M NSCLC, with 1 partial response reported[17].

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

NOTE Clinical trials are ordered by gene and prioritized in the following descending order: pediatric trial qualification → Geographical proximity → Later trial phase → Trial verification within last 2 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 meant to be a complete list of available trials and does not necessarily indicate that the patient will meet clinical trial enrollment criteria. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov.

GENE

EGFR

ALTERATION

exon 19 deletion (E746_A750del), T790M, amplification

RATIONALE

EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Several strategies to overcome resistance are under investigation, including next-generation EGFR TKIs and EGFR inhibitor combinations. On basis of extensive clinical evidence, EGFR T790M confers resistance to first generation EGFR tyrosine kinase inhibitors. Studies have also reported resistance to afatinib and lapatinib. Other agents may be relevant, including irreversible EGFR inhibitors, and in the context of lung cancer, the ALK/EGFR/ROS1 inhibitor brigatinib.

NCT03521154

PHASE 3

A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer (LAURA)

TARGETS EGFR

LOCATIONS: Törökbálint (Hungary), Mátraháza (Hungary), Istanbul (Turkey), Izmir (Turkey), Adapazari (Turkey), Ankara (Turkey), Barcelona (Spain), Adana (Turkey), San Sebastián (Spain), Valencia (Spain)

NCT02609776

PHASE 1

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

TARGETS MET, EGFR

LOCATIONS: Milano (Italy), Marseille (France), Lyon Cedex 8 (France), Dijon (France), Villejuif Cedex (France), Paris (France), Barcelona (Spain), Bordeaux (France), Sutton (United Kingdom), Saint-Herblain Cedex (France)

NCT03333343

PHASE 1

Study of EGF816 in Combination With Selected Targeted Agents in EGFR-mutant NSCLC

TARGETS EGFR, CDK6, CDK4, ARAF, BRAF, MET, MEK

LOCATIONS: Ancona (Italy), Milano (Italy), Rozzano (Italy), Koeln (Germany), Essen (Germany), Toronto (Canada), Shatin, New Territories (Hong Kong), Taipei (Taiwan), Tainan (Taiwan), Singapore (Singapore)

NCT04075396

PHASE 1/2

A Study of YH25448 in Participants With Epidermal Growth Factor Receptor (EGFR) Mutation Positive Advanced Non-Small Cell Lung Cancer (NSCLC)

TARGETS EGFR

LOCATIONS: Barcelona (Spain), Madrid (Spain), Malaga (Spain), Florida

NCT03865511

PHASE 2

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

TARGETS EGFR

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

NCT03804580

PHASE 2

First-line Treatment With Osimertinib in EGFR-mutated Non-small Cell Lung Cancer, Coupled to Extensive Translational Studies

TARGETS
EGFR

LOCATIONS: Vilnius (Lithuania), Copenhagen (Denmark), Odense (Denmark), Aarhus (Denmark), Stockholm (Sweden), Drammen (Norway), Oslo (Norway), Trondheim (Norway)

NCT03260491

PHASE 1

U3-1402 in Metastatic or Unresectable Non-Small Cell Lung Cancer

TARGETS
ERBB3

LOCATIONS: Amsterdam (Netherlands), Barcelona (Spain), Massachusetts, New York, Tennessee, Georgia, Taipei (Taiwan), Washington, Tainan (Taiwan), Osaka (Japan)

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Birmingham (United Kingdom), Bristol (United Kingdom), Sheffield (United Kingdom)

NCT03516214

PHASE 1

EGF816 and Trametinib in Patients With Non-small Cell Lung Cancer and T790M-positive Resistance to EGFR TKI Therapy

TARGETS
MEK, EGFR

LOCATIONS: Dresden (Germany), Würzburg (Germany), Cologne (Germany), Essen (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), Villejuif (France), Massachusetts, Virginia, Michigan, North Carolina, Illinois, Tennessee, Taipei City (Taiwan), Colorado

FoundationOne Liquid interrogates the complete exonic sequence of 35 genes, introns of 7 genes involved in rearrangements, and select exons of an additional 35 genes. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

APC	*AR*	*ATM*	*BRCA1*	*BRCA2*	*CCND1*	*CD274 (PD-I1)*	*CDH1*	*CDK4*
CDK6	*CDK12*	*CDKN2A*	*CHEK2*	*CRKL*	*EGFR*	*ERBB2*	*ERRFI1*	*FGFR1*
FGFR2	*FOXL2*	*KRAS*	*MDM2*	*MET*	*MYC*	*MYCN*	*NF1*	*PALB2*
PDCD1LG2 (PD-L2)	*PTEN*	*PTPN11*	*RB1*	*SMO*	*STK11*	*TP53*	*VEGFA*	

DNA GENE LIST: SELECT EXONIC SEQUENCE OF THE DETECTION OF BASE SUBSTITUTIONS, INSERTIONS/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1 *Exons 4-9*	*AKT1* *Exon 3*	*ALK* *Exons 20-29*	*ARAF* *Exons 4, 5, 7, 11, 13, 15, 16*	*BRAF* *Exons 11-18*	*BTK* *Exons 2, 15*	*CTNNB1* *Exon 3*	*DDR2* *Exons 5, 17, 18*	*ESR1* *Exons 4-8*
EZH2 *Exons 4, 16, 18*	*FGFR3* *Exons 7, 9, 14*	*FLT3* *Exons 14, 15, 20*	*GNA11* *Exons 4, 5*	*GNAQ* *Exons 4, 5*	*GNAS* *Exons 1, 8*	*HRAS* *Exons 2, 3*	*IDH1* *Exon 4*	*IDH2* *Exon 4*
JAK2 *Exon 14*	*JAK3* *Exons 5, 11-13, 15, 16*	*KIT* *Exons 8, 9, 11-13, 17*	*MAP2K1 (MEK1)* *Exons 2, 3*	*MAP2K2 (MEK2)* *Exons 2-4, 6, 7*	*MPL* *Exon 10*	*MTOR* *Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56*	*MYD88* *Exon 4*	*NPM1* *Exons 4-6, 8, 10*
NRAS *Exons 2, 3*	*PDGFRA* *Exons 12, 18*	*PDGFRB* *Exons 12-21, 23*	*PIK3CA* *Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)*	*RAF1* *Exons 3-7, 10, 14, 15, 17*	*RET* *Exons 11, 13-16*	*ROS1* *Exons 36-38, 40*	*TERT* *(Promoter only)*	

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*EGFR*	*FGFR2*	*FGFR3*	*PDGFRA*	*RET*	*ROS1*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite Status (MS)

The 85th percentile redundant coverage for this sample is 4,588x

PERFORMANCE SPECIFICATIONS

	Mutant Allelle Frequency (MAF) / Tumor Fraction‡	Sensitivity*	Positive Predictive Value (PPV)*
Base Substitutions	>0.5%	99.9% (99.7%-99.9%)	100% (99.9%-100%)
	0.25%-0.5%	95.8% (94.5%-96.9%)	99.8% (99.3%-99.9%)
	<0.25%	68.4% (65.7%-70.9%)	96.1% (94.8%-97.1%)
Insertions/Deletions†	>0.5%	99.7% (98.7%-99.9%)	100% (99.3%-100%)
	0.25%–0.5%	87.7% (81.1%-92.2%)	98.8% (95.4%-99.8%)
	<0.25%	60.5% (52.7%-67.7%)	96.8% (92.3%-98.8%)
Rearrangements**	>0.5%	100% (85.9%-100%)	100% (85.9%-100%)
	0.25%–0.5%	89.4% (65.5%-98.2%)	100% (77.1%-100%)
	<0.25%	68.4% (43.5%-86.4%)	100% (71.7%-100%)
Copy Number Amplifications§	≥20%	95.3% (82.9%-99.2%)	97.6% (85.9%-99.9%)
	<20%	Varies depending on amplitude of CNA and ctDNA fraction	
MSI¶	>2.0%	92.0% (72.5%-98.6%)	100% (82.2%-100%)

Reproducibility (average concordance between replicates)	
97.7% inter-batch precision	95.9% intra-batch precision

*95% confidence intervals. Sensitivity assessment for <0.25% bin restricted to alterations in the 0.125%-0.25% expected allele frequency range.

†Deletions up to 2kb and insertions up to 40bp are detected. Sensitivity is lower for indels in repetitive regions.

**Performance for gene fusions within targeted introns only. Sensitivity for gene fusions occurring outside targeted introns or in highly repetitive intronic sequence contexts is reduced.

‡Sensitivity for MSI and copy number amplifications was determined using contrived samples with tumor fraction >20%. Most clinical samples will have less than 20% tumor fraction.

§Copy-number ≥8.

¶Microsatellite status, which is a measure of microsatellite instability (MSI), is determined by assessing indel characteristics at a subset of homopolymer repeat loci covered by the assay. Microsatellite status is assayed for all FoundationOne®Liquid samples and will only be reported if MSI-High is determined.

Assay specifications are based on samples meeting a minimum coverage threshold (85% of targeted regions must have 2500× redundant coverage). Specimens with higher input mass typically obtain higher coverage and have higher sensitivity for low-frequency alterations.

For additional information specific to the performance of this specimen, please contact Foundation Medicine, Inc. at 1-888-988-3639.

ABOUT FOUNDATIONONE®LIQUID

FoundationOne Liquid was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne Liquid may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

DIAGNOSTIC SIGNIFICANCE

FoundationOne Liquid identifies alterations to select cancer-associated genes or portions of genes (biomarkers).

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.

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.

RANKING OF ALTERATIONS AND THERAPIES

Biomarker and Genomic Findings

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

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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.

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 is performed using cell-free DNA, and as such germline events may not be reported. The following target typically has low coverage resulting in a reduction in sensitivity: *TP53* exon 1 and *PDGFRA* exon 12.

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

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