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

DATE OF BIRTH 13 December 1935
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Oncologia Patologica
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 320946
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN ID OC 12/13/1935
SPECIMEN TYPE Blood
DATE OF COLLECTION 04 June 2021
SPECIMEN RECEIVED 09 June 2021

Sensitivity for the detection of alterations and genomic signatures is reduced and the TMB score may be underreported.

Biomarker Findings

Blood Tumor Mutational Burden - Cannot Be Determined
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Cannot Be Determined

Genomic Findings

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

EGFR amplification - equivocal, L858R†
NF1 L2668fs*11
MET C385Y
DNMT3A W306*
TET2 splice site 3955-1G>A
TP53 Q38*

† See About the Test in appendix for details.

9 Therapies with Clinical Benefit
0 Therapies with Lack of Response
28 Clinical Trials

BIOMARKER FINDINGS

Blood Tumor Mutational Burden - Cannot Be Determined

Microsatellite status - MSI-High Not Detected

Tumor Fraction - Cannot Be Determined

GENOMIC FINDINGS

		VAF %
EGFR -	amplification - equivocal	-
	L858R	26.6%

10 Trials see p. 17

THERAPY AND CLINICAL TRIAL IMPLICATIONS

Unable to determine bTMB status due to low evidence of tumor DNA.

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

Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.

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

NCCN category

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GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
NF1 -	L2668fs*11	17.4%	None	Selumetinib
				Trametinib
10 Trials see p. 21				
MET -	C385Y	2.1%	None	None
10 Trials see p. 19				

☐ *NCCN category*

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

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

DNMT3A - W306* p. 8 ***TET2*** - splice site 3955-1G>A p. 9

GENOMIC FINDINGS 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.

DNMT3A - W306* p. 8
TET2 - splice site 3955-1G>A p. 9
TP53 - Q38* p. 10

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved 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*, *BRCA1*, *BRCA2*, *BRIP1*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF2*, *PALB2*, *PMS2*, *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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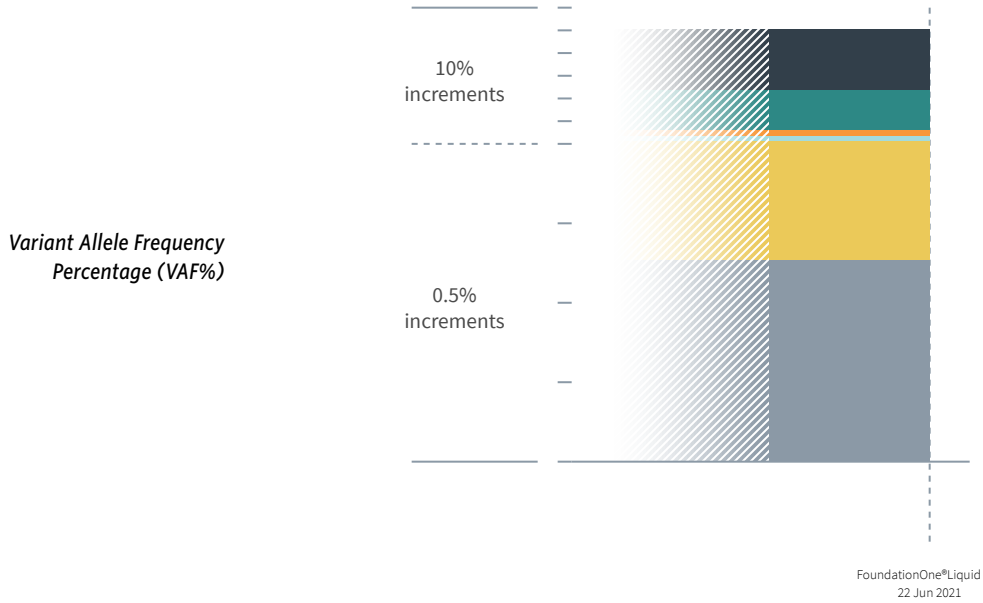

HISTORIC PATIENT FINDINGS		ORD-1110473-01 VAF%
Blood Tumor Mutational Burden		Cannot Be Determined
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Cannot Be Determined
EGFR	● L858R	26.6%
	amplification	Detected
NF1	● L2668fs*11	17.4%
MET	● C385Y	2.1%
DNMT3A	● W306*	2.3%
TET2	● splice site 3955-1G>A	1.3%
TP53	● Q38*	2.7%

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

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

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

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

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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
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4]. As the bTMB status of this tumor cannot be determined with confidence, the benefit of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)[3]. Published data investigating the prognostic implications of bTMB levels in lung cancer are limited (PubMed, Jul 2020). A large study of Chinese patients with 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)[5]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[6]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[6-7].

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[8-9] and cigarette smoke in lung cancer[10-11], treatment with temozolomide-based chemotherapy in glioma[12-13], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[14-18], and microsatellite instability (MSI)[14,17-18]. The bTMB level in this sample could not be determined with confidence. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

Specimens with high 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 tumor fraction is not detected as high, 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[19-24].

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)[25]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[26], Ewing sarcoma and osteosarcoma[27], prostate cancer[22], breast cancer[28], leiomyosarcoma[29], esophageal cancer[30], colorectal cancer[31], and gastrointestinal cancer[32].

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[33], 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[34-35]. However, the tumor fraction estimate in this sample could not be determined with confidence.

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GENE
EGFR

ALTERATION
amplification - equivocal, L858R

TRANSCRIPT ID
NM_005228

CODING SEQUENCE EFFECT
2573T>G

POTENTIAL TREATMENT STRATEGIES

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[36], gefitinib[37], afatinib[38], dacomitinib[39], and osimertinib[40]; however, the data for patients with other tumor types are limited[41-46]. Third-generation EGFR inhibitors, such as osimertinib, selectively target mutated EGFR, including EGFR T790M[40,47]. A Phase 2 study of the third-generation TKI D-0316 for patients with EGFR T790M-mutated non-small cell lung cancer (NSCLC) reported an ORR of 65% (188/290) and a DCR of 95% (276/290); 53% (18/34) of patients with brain metastases at enrollment achieved intracranial PR[48]. Osimertinib achieved a 61% (78/127) ORR for T790M-positive cases and a 21% (13/61) ORR for T790M-negative cases[40]. In a Phase 1 study, the third-generation EGFR inhibitor alflutinib achieved a 77% (89/116) ORR for the dose expansion cohort, as well as a CNS ORR of 59% (10/17) for patients with T790M-positive NSCLC[49]. Resistance to EGFR inhibition may arise from reactivation of the MAPK pathway, and preclinical evidence suggests that co-targeting EGFR and MAPK signaling may impede the development of acquired resistance to third-generation EGFR inhibitors[50-52]. A Phase 1 trial of the EGFR and MET bispecific antibody amivantamab for EGFR-mutated NSCLC reported a 30% (32/108) ORR for patients with various EGFR mutation types[53]. The same trial combining amivantamab with the third-generation EGFR inhibitor lazertinib elicited an ORR of 36% (16/45) for the osimertinib-resistant, chemotherapy-naive cohort, as well as an ORR of 100% (20/20) for the treatment-naive cohort[54]. EGFR amplification or expression may be associated with benefit from anti-EGFR antibodies, such as cetuximab[55-58], panitumumab[56], or necitumumab[59]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin[60-61] that has also shown benefit in patients with CRC and melanoma[62-63]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy[64-67]. Preclinical studies have reported that EGFR-mutant cells[64-66], including cells with exon 20 insertions[68], are sensitive to HSP90 inhibitors. In a Phase 1 trial, the HER3-targeted antibody patritumab deruxtecan elicited an ORR of 25% (14/56) and a DCR of 69.6% (39/56) for patients with non-small cell lung cancer (NSCLC) previously treated with an EGFR TKI and platinum-based chemotherapy, many of whom displayed TKI resistance alterations[69]. 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[70-71]. 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[72]. The reovirus Reolysin targets cells with activated RAS signaling[73-75] 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[76-84]. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear[85]. Although meta-analyses demonstrate that increased EGFR copy number is significantly associated with improved ORR, PFS, and OS on first-generation EGFR TKIs[86-89], the magnitude of clinical benefit is limited for patients with EGFR amplification and without sensitizing EGFR mutations when comparing first-or second generation EGFR TKIs to control treatment[90-95]. In the Phase 3 IPASS trial, patients with unmutated, amplified EGFR had a significantly shorter PFS when treated with gefitinib as compared to carboplatin/paclitaxel (HR 3.85; 95% CI, 2.09 to 7.09)[90]. Biomarker analysis of the LUX-Lung 8 trial in squamous NSCLC, which included only a small subset of patients with EGFR mutations (6%), did not observe a significant association of EGFR expression with outcomes on afatinib or erlotinib[96]. A retrospective study in China reported that EGFR amplification was associated with a significantly improved median PFS (5.0 vs 2.0 months) and a similar median OS (16.6. vs. 15.4 months) for patients with unmutated EGFR treated with gefitinib or erlotinib[97]. The Phase 3 IMpower150 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[98]; 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[99-103]. EGFR mutation has been reported in 12-36% of lung adenocarcinomas[99,104-105] and in 4% of lung squamous cell carcinomas[100]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[101-103,106-108]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[109-110]. In patients with lung adenocarcinoma, EGFR gene amplification was a predictor of poor disease-free survival[111]. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[111-112]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[113] or resected Stage 1 NSCLC[114]. Nuclear expression of EGFR in NSCLC has been reported to associate with higher disease stage, shorter progression-free survival, and shorter overall survival[115].

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[116]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[102,117-118]. EGFR L858 is located in the kinase domain and is encoded by exon 21. EGFR L858R has been characterized as activating[119-121] and patients with the L858R mutation have been shown to be sensitive to EGFR tyrosine kinase inhibitors, such as erlotinib, gefitinib[119-121], and afatinib[122].

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GENE
NF1

ALTERATION
L2668fs*11

TRANSCRIPT ID
NM_001042492

CODING SEQUENCE EFFECT
8002delC

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in neurofibromatosis type 1[123-124] and neurofibromatosis-associated glioma or glioblastoma[125-126], as well as extensive preclinical evidence in several tumor types[127-132], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including the approved agents everolimus and temsirolimus, based on limited clinical data[133-135] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[136-137]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[138]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[139], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[140]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In the TCGA datasets, NF1 mutation has been observed in 11% of lung adenocarcinoma cases[99] and 8% of lung squamous cell carcinoma cases[100]. Published data investigating the prognostic implications of NF1 alteration in lung cancer are limited (PubMed, Feb 2021). However, decreased NF1 expression was reported in 2 lung adenocarcinoma samples after disease progression on first generation EGFR inhibitor and afatinib; neither sample harbored EGFR T790M mutation[141].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[142]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[143]. The consequences of alterations that may leave the GAP-related domain intact, such as seen here, are unclear; however, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[144-146]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[147-148], and in the appropriate clinical context, germline testing of NF1 is recommended.

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GENE
MET

ALTERATION
C385Y

TRANSCRIPT ID
NM_000245

CODING SEQUENCE EFFECT
1154G>A

POTENTIAL TREATMENT STRATEGIES
On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. MET inhibitors crizotinib, capmatinib, PF-04217903, tepotinib, glesatinib, savolitinib, and foretinib have provided benefit for patients with MET-mutated papillary renal cell carcinoma (RCC)[149-152], histiocytic sarcoma[153], and non-small cell lung cancer (NSCLC) of varied histologies[154-158]. Patients with MET exon 14 mutated NSCLC who were treated with 1 of several MET inhibitors exhibited superior outcomes (median OS 24.6 vs. 8.1 months; HR=0.11, p=0.04) compared with patients who were not treated with a MET inhibitor[159]. Tepotinib showed durable clinical activity in patients with NSCLC with MET exon 14 skipping mutations[160], and yielded a PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC[161]. In another study, 11 patients with hereditary papillary RCC and germline MET mutations (4 of which were H1094R) experienced 5 PRs and 5 SDs after treatment with foretinib[149]. Savolitinib yielded ORRs of 49% (30/61) in patients with MET exon 14 mutated NSCLC[162] and numerically higher ORR for patients with MET-driven papillary RCC compared to sunitinib (27% [9/33] vs. 7.4% [2/27])[152]. A Phase 1 study for patients with MET-altered NSCLC treated with MET inhibitor bozitinib monotherapy reported an overall ORR of 30.6% (11/36) and DCR of 97.2% (35/36) with MET overexpression, amplification, and exon 14 skipping demonstrating ORRs of 35.7% (5/14), 41.2% (7/17), and 66.7% (10/15), respectively; increased ORRs were observed in patients with both exon 14 skipping and amplification (100%, 4/4) and with both amplification and overexpression (50%, 3/6)[163]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS
In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in 3% of samples[153]. In TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[99-100]. Studies on the effect of MET amplification on prognosis in NSCLC have yielded conflicting results[101,164-170], although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[171]. MET exon 14 splice alteration, which has predominantly been observed in lung cancer, was found to be an independent poor prognostic factor in a study of 687 patients with NSCLC[172]. However, other studies did not find MET exon 14 splice alteration as a major risk factor for overall survival for NSCLC patients, although recurrence rate was significantly higher in patients with exon 14 splice alteration compared to those with ALK fusion[173-174]. Among NSCLC patients with exon 14 alterations that had not been previously treated with a MET inhibitor, a non-significant trend for reduced survival was noted in the context of concurrent MET amplification (5.2 vs 10.5 months, p = 0.06)[159].

FINDING SUMMARY
MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[175-176]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
DNMT3A

ALTERATION
W306*

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
917G>A

POTENTIAL TREATMENT STRATEGIES
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 2021)[177-178]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2021).

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[179-180]. 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[181-186]. Alterations such as seen here may disrupt DNMT3A function or expression[187-190].

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[191-196]. 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[191-192]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[197]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[195,198-199]. 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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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
TET2

ALTERATION
splice site 3955-1G>A

TRANSCRIPT ID
NM_001127208

CODING SEQUENCE EFFECT
3955-1G>A

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

FREQUENCY & PROGNOSIS
TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2021)[177-178]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2021).

FINDING SUMMARY
TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[200-201]. Alterations such as seen here may disrupt TET2 function or expression[202-206].

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[191-196]. 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[191-192]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[197]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[195,198-199]. 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
TP53

ALTERATION
Q38*

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
112C>T

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[207-210], or p53 gene therapy and immunotherapeutics such as SGT-53[211-215] and ALT-801[216]. 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[217]. 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[218]. 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[219]. 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[220]. 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[221]. 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[222]. 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[215]. 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[223]. 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[224-225]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[226-227]. 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)[99-100,228-233], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[99-100,105,234]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[177-178]. 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[235]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[236].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[237]. Alterations such as seen here may disrupt TP53 function or expression[238-242].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[243-245], including sarcomas[246-247]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[248] to 1:20,000[247]. 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[249]. 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[191-196]. 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[191-192]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[197]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[195,198-199]. 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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Afatinib

Assay findings association

EGFR
amplification - equivocal, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[38-39,250-251] , whereas data for patients with other tumor types are limited[41-46,252] .

SUPPORTING DATA

Afatinib enabled 1 PR and 1 SD for 2 patients with EGFR-amplified NSCLC in a Phase 2 study[92]. Afatinib has shown significant clinical activity for patients with NSCLC and the EGFR common sensitizing mutations L858R or exon 19 deletions, based on extensive clinical evidence[38,250,253-256] . Two randomized Phase 3 trials reported significantly improved median PFS from afatinib compared with chemotherapy for patients with EGFR common sensitizing mutations (LUX-Lung 3, 13.6 vs. 6.9 months, HR 0.47, p<0.001; LUX-Lung 6, 11.0 vs. 5.6 months, HR 0.28, p<0.0001)[38,250] . However, while afatinib significantly increased OS relative to chemotherapy for patients with EGFR exon 19 alterations in these two trials (LUX-Lung 3, 33.3 vs. 21.1 months, HR=0.54; LUX-Lung 6, 31.4 vs. 18.4 months, HR=0.64), no significant OS differences were observed in treatment for patients with L858R mutation[122]. A similar alteration-specific difference was observed for EGFR-mutated treatment-naive NSCLC in a retrospective analysis, which reported numerically longer median OS from second- versus first-generation EGFR TKIs (48.8 vs. 26.4 months, HR=0.59) for patients with exon 19 deletions, but no substantial difference for patients with L858R (25.4 vs. 20.6 months, HR=0.90)[253]. A Phase 2b study of first-line afatinib compared with gefitinib, also for NSCLC with exon 19 deletions or L858R, reported similar median OS for the two therapies (27.9 vs. 24.5 months, HR=0.86) but significantly longer time-to-treatment-failure (13.7 vs. 11.5 months, HR=0.75) and higher ORR (73% vs. 56%, p=0.0018) with afatinib[254]. Patients with metastatic NSCLC and common EGFR mutations who progressed on prior chemotherapy experienced an ORR of 50.0% (30/60) from afatinib in a Phase 4 trial[255]. As first-line therapy for NSCLC with EGFR exon 19 deletions or L858R, prospective or randomized Phase 2 trials have reported a median PFS of 10.2 months and OS of 24.8 months for patients unfit for chemotherapy[256] and an ORR of 72.5% (n=40, 1 CR), DCR of 100% (40/40), and median PFS and OS of 15.2 and 30.0 months, respectively, for elderly patients ≥70 years old[257]. A retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 27.4% (63/230) for patients with common sensitizing EGFR mutations and an ORR of 24.4% (105/431) for the entire cohort[258]. In a case report, a patient with NSCLC with exon 19 deletion and leptomeningeal metastases experienced an ongoing 16-month PR from afatinib in extracranial, brain, and leptomeningeal lesions[259]. 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%[92,260-264] ; however, DCRs of more than 50% have been observed[92]. 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[265] or osimertinib[266], respectively. Extensive clinical data have demonstrated that afatinib is effective for patients with EGFR-mutated advanced NSCLC, including exon 19 deletions and L858 mutations, as well as uncommon sensitizing mutations in exons 18 or 20[38,122,250,254,256,258,267] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[92,268-278] . The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer median OS (7.9 vs. 6.8 months, HR=0.81), significantly longer median PFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[267]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[279].

Dacomitinib

Assay findings association

EGFR
amplification - equivocal, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[38-39,250-251] , whereas data for patients with other tumor types are limited[41-46,252] . Patients with untreated advanced NSCLC and EGFR L858R mutations achieved an ORR of 73% (68/93)[280] and a median OS of 32.5 months with dacomitinib[39].

SUPPORTING DATA

A randomized Phase 3 trial in patients with NSCLC with activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS, 34.1 vs. 26.8 months, HR=0.760; median PFS, 14.7 vs. 9.2 months, HR=0.59)[280-281] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[282]. A pooled subgroup analysis of patients with NSCLC with activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (median PFS, 14.6 vs, 9.6 months, HR=0.717; median OS, 26.6 vs, 23.2 months, HR=0.737)[283]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[284-286] . 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[287]. A Phase 2 study of dacomitinib in patients with NSCLC who had been previously treated with chemotherapy or erlotinib and were not selected for EGFR mutations reported an ORR of 4.5% (3/66)[285]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[288].

Erlotinib

Assay findings association

EGFR
amplification - equivocal, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[36,289-291] . For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival[292-296] .

SUPPORTING DATA

The Phase 3 BR.21 trial demonstrated prolonged OS for genomically unselected patients with NSCLC treated with erlotinib compared with those treated with standard chemotherapy[297]. 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)[36]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[298]. 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[299]. 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)[289]. 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[290]. 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)[300]. 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[301].

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Gefitinib

Assay findings association

EGFR
amplification - equivocal, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[291,302-307] , and responses have been reported for patients with EGFR-rearranged NSCLC[308-309] . For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival[292-296] . Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant overall survival benefit from gefitinib compared to placebo (HR = 0.21)[292,310] .

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)[304] 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)[311]. 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[37]. 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[90,305] . 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[312-313] . 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[314]. 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[315].

Osimertinib

Assay findings association

EGFR
amplification - equivocal, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR TKI-sensitizing mutations or rearrangements and/or the EGFR T790M mutation may predict sensitivity to osimertinib in non-small cell lung cancer[40,47,308,316-317] . 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[47].

SUPPORTING DATA

The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (mPFS; 18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months, HR=0.80) for patients with advanced non-small cell lung cancer (NSCLC) and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858)[47,318] . In the Phase 3 ADAURA study, patients with early-stage EGFR-mutated NSCLC receiving adjuvant osimertinib experienced both longer disease-free survival (DFS; not reached vs. 19.6 months, HR=0.17) and central nervous system DFS (not reached vs. 48.2 months, HR=0.18) than those receiving placebo[319]. A Phase 1 study reported that T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and mPFS of 2.8 months[40]. A Phase 1/2 trial of osimertinib in combination with bevacizumab for patients with untreated metastatic EGFR-mutated non-small cell lung cancer (NSCLC) reported an 80% (39/49) ORR, a 100% (6/6, 2 CRs) central nervous system response rate, median PFS of 19 months, and a 1-year PFS rate of 72%[320]. 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[321].

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Cetuximab

Assay findings association

EGFR
amplification - equivocal, L858R

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). 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[56].

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[55]. 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[322]. 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[323]. 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%)[324]. 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[325]; however, in this study a patient identified with an exon 19 deletion and T790M progressed rapidly on cetuximab and erlotinib[326].

Panitumumab

Assay findings association

EGFR
amplification - equivocal, L858R

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[56].

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[327], and subsequent studies investigating the addition of panitumumab to pemetrexed/cisplatin reported no benefit for patients with wild-type KRAS lung adenocarcinoma[328]. The combination of afatinib and panitumumab has been explored for 2 patients with EGFR T790M NSCLC, with 1 partial response reported[329].

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Selumetinib

Assay findings association

NF1
L2668fs*11

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[123,126] and strong preclinical evidence[128-132] , NF1 inactivation may predict sensitivity to MEK inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

In a Phase 2 study of selumetinib monotherapy to treat patients with lung cancer who were selected for mutation in KRAS, HRAS, NRAS, or BRAF, a mPFS of 2.3 months and mOS of 6.5 months was observed[330]. In a Phase 2 study of patients with NSCLC who had failed on at least 2 prior chemotherapeutic regimes, selumetinib as a monotherapy did not improve survival as compared to pemetrexed (67 vs 90 days, HR= 1.08); however, 2 PRs were reported[331]. A Phase 2 study of selumetinib combined with docetaxel in patients with advanced or metastatic KRAS wild-type NSCLC who were previously treated did not report improved survival benefit compared to docetaxel alone[332]. A Phase 2 study of selumetinib combined with pemetrexed and platinum based chemotherapy for treatment of patients with advanced non-squamous NSCLC showed improved ORR (35% with intermittent dosing and 62% for continuous dosing) compared to chemotherapy alone (24%) but did not report a statistically significant improvement in mPFS[333]. The combination of selumetinib with platinum doublet chemotherapy has been studied in a Phase 1 trial for patients with advanced NSCLC in the first line setting and has reported 4/21 PRs in the selumetinib + pemetrexed/carboplatin cohort and 2/15 PRs in the pemetrexed/cisplatin cohort; selumetinib in combination with gemcitabine regimens was not tolerated[334]. A Phase 1b study of selumetinib in combination with osimertinib for patients with EGFR-mutated lung cancer who had progressed on previous TKI treatment reported an ORR of 41.7% (15/36)[321].

Trametinib

Assay findings association

NF1
L2668fs*11

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[123,126] and strong preclinical evidence[128-132] , NF1 inactivation may predict sensitivity to MEK inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

For patients with previously treated BRAF V600E-mutated metastatic NSCLC, trametinib in combination with the BRAF inhibitor dabrafenib achieved an ORR of 63% (36/57), including 2 CRs and 34 PRs, a DCR (CRs, PRs, and SD) of 79% (45/57), and a median PFS of 9.7 months[335]. Dabrafenib plus trametinib demonstrated similar activity as first-line therapy for BRAF V600E-mutated metastatic NSCLC, with an ORR of 64% (23/36) and a median PFS of 10.9 months[336]. Phase 1 and 2 monotherapy trials of MEK inhibitors such as trametinib and RO4987655 have shown low response rates in patients with NSCLC, irrespective of KRAS mutation status, and no improvement in PFS compared to docetaxel[337-339] . However, Phase 1 and 2 trials of MEK inhibitors in combination with docetaxel or pemetrexed in NSCLC have shown improved clinical activity and patient survival compared to chemotherapeutics alone, although no association was observed between response and KRAS mutation status[340-342] . In contrast, although 3 objective responses were observed in patients with NSCLC treated with the MEK inhibitor selumetinib in combination with erlotinib in a Phase 2 trial, there was no significant increase in either PFS or OS relative to patients treated with selumetinib alone; further, the combination increased toxicity relative to monotherapy[343]. Preclinical and early clinical studies have shown synergistic antitumorigenic effects when the combination of MEK and PI3K inhibitors was used to treat KRAS-driven NSCLC[344-346] . A Phase 1b combination trial of trametinib and the pan-PI3K inhibitor BKM120 reported a DCR of 59% in patients with NSCLC, including 1 confirmed PR in 17 patients; although the reported adverse effects were prevalent and often severe, the study recommended a Phase 2 dose[347]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[139], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[140].

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

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

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.

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ORDERED TEST # ORD-1110473-01

CLINICAL TRIALS

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
amplification - equivocal, L858R

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

NCT04487080

PHASE 3

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

TARGETS
MET, EGFR

LOCATIONS: Monza (Italy), Milano (Italy), Rozzano (Italy), Ravenna (Italy), Meldola (Italy), La Tronche (France), Bron (France), Marseille Cedex 20 (France), Farkasgyepü (Hungary), Napoli (Italy)

NCT04077463

PHASE 1

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

TARGETS
EGFR, MET

LOCATIONS: Milano (Italy), Ravenna (Italy), Gauting (Germany), Stuttgart (Germany), Lyon Cedex 8 (France), Marseille (France), Napoli (Italy), Köln (Germany), Halle (Saale) (Germany), Hemer (Germany)

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: Rozzano (Italy), Koeln (Germany)

NCT04035486

PHASE 3

A Study of Osimertinib With or Without Chemotherapy as 1st Line Treatment in Patients With Mutated Epidermal Growth Factor Receptor Non-Small Cell Lung Cancer (FLAURA2)

TARGETS
EGFR

LOCATIONS: Lyon (France), Praha (Czechia), Praha 5 (Czechia), Olomouc (Czechia), Banska Bystrica (Slovakia), Ostrava - Vitkovice (Czechia), Creteil (France), Villejuif Cedex (France), Poprad (Slovakia), Kosice (Slovakia)

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: Pécs (Hungary), Székesfehérvár (Hungary), Törökbálint (Hungary), Budapest (Hungary), Gyöngyös - Mátraháza (Hungary), Barcelona (Spain), San Sebastián (Spain), Valencia (Spain), Madrid (Spain), Izmir (Turkey)

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NCT04248829

PHASE 3

Clinical Trial of YH25448(Lazertinib) as the First-line Treatment in Patients With EGFR Mutation Positive Locally Advanced or Metastatic NSCLC (LASER301)

TARGETS
EGFR

LOCATIONS: Székesfehérvár (Hungary), Tatabánya (Hungary), Törökbálint (Hungary), Budapest (Hungary), Sremska Kamenica (Serbia), Belgrade (Serbia), Kragujevac (Serbia), Debrecen (Hungary), Niš (Serbia), Úzhgorod (Ukraine)

NCT03944772

PHASE 2

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

TARGETS
EGFR, MET, PD-L1

LOCATIONS: Maastricht (Netherlands), Nijmegen (Netherlands), Barcelona (Spain), Rotterdam (Netherlands), Amsterdam (Netherlands), Odense C (Denmark), Vejle (Denmark), Herlev (Denmark), Madrid (Spain), A Coruña (Spain)

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)

NCT02609776

PHASE 1

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

TARGETS
MET, EGFR

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

NCT03810066

PHASE 2

Exploring the Theragnostic Value of Osimertinib in EGFR-mutated Lung Cancer (THEROS)

TARGETS
EGFR

LOCATIONS: Essen (Germany)

GENE
MET

ALTERATION
C385Y

RATIONALE
Activation of MET may lead to increased MET expression and activation and may therefore confer sensitivity to MET inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT03539536

PHASE 2

Study of Telisotuzumab Vedotin (ABBV-399) in Subjects With Previously Treated c-Met+ Non-Small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Parma (Italy), Meldola (Italy), Orbassano (Italy), Gauting (Germany), Rome (Italy), Strasbourg (France), Bron (France), Lyon CEDEX 08 (France), Marseille (France), Farkasgyepu (Hungary)

NCT03170960

PHASE 1/2

Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-L1, MET, RET, ROS1, VEGFRs

LOCATIONS: Milano (Italy), Rozzano (Italy), Pavia (Italy), Meldola (Italy), Nice Cedex 02 (France), Tübingen (Germany), Roma (Italy), Strasbourg (France), Vandoeuvre les nancy (France), Lyon Cedex 08 (France)

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, RET, ROS1, VEGFRs

LOCATIONS: Nice (France), Lyon (France), Marseille (France), Toulouse (France)

NCT02099058

PHASE 1

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

TARGETS
MET, EGFR, PD-1

LOCATIONS: Marseille CEDEX 05 (France), Massachusetts, New York, New Jersey, Virginia, Michigan, Illinois, Tennessee, Colorado, Texas

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), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Maine

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

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

NCT01639508

PHASE 2

Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity

TARGETS
MET, RET, ROS1, VEGFRs

LOCATIONS: New York, New Jersey

NCT02795156

PHASE 2

Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations

TARGETS
BRAF, KIT, RET, VEGFRs, EGFR, ERBB2, ERBB4, MET, ROS1

LOCATIONS: Wisconsin, Tennessee, Florida, Missouri, Colorado

NCT03666143

PHASE 1

A Phase 1b Study to Assess Sitravatinib in Combination With Tislelizumab in Patients With Advanced Solid Tumors.

TARGETS
AXL, DDR2, FLT3, KIT, MET, PDGFRA, RET, TRKA, TRKB, VEGFRs, PD-1

LOCATIONS: Beijing (China), Tianjin (China), Hangzhou (China), Guangzhou (China), Perth (Australia), South Brisbane (Australia), Melbourne (Australia), Heidelberg (Australia), Blacktown (Australia)

GENE
NF1

ALTERATION
L2668fs*11

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

NCT03600701

PHASE 2

Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer

TARGETS
PD-L1, MEK

LOCATIONS: New Hampshire, District of Columbia, Virginia, Michigan, Ohio, North Carolina, Alabama, Florida, Oklahoma

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Massachusetts, New York, Pennsylvania, Maryland, Virginia, Michigan, Ohio, Illinois, Wisconsin, North Carolina

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Texas, Nedlands (Australia), Melbourne (Australia), Blacktown (Australia), Randwick (Australia)

NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

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

NCT04250545

PHASE 1

Testing of the Anti Cancer Drugs CB-839 HCl (Telaglenastat) and MLN0128 (Sapanisertib) in Advanced Stage Non-small Cell Lung Cancer

TARGETS
mTORC1, mTORC2, GLS

LOCATIONS: New York, California

NCT01737502

PHASE 1/2

Sirolimus and Auranofin in Treating Patients With Advanced or Recurrent Non-Small Cell Lung Cancer or Small Cell Lung Cancer

TARGETS
mTOR

LOCATIONS: Florida

NCT01582191

PHASE 1

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

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

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

ASXL1
R413Q

BARD1
P464S

EGFR
V1010D

KMT2A (MLL)
A53V

MAP3K1
L78P

SPEN
S2306del

TSC1
K587R

TSC2
A42G and A460T

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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)	***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**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*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**	*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	*FAM46C*	*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*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*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)

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KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*
MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***
MITF	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*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**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARK2	*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*	*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*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*
TGFBR2	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*	*TYRO3*
U2AF1	***VEGFA***	*VHL*	*WHSC1*	*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 detects select genomic rearrangements, select copy number alterations, 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 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.

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 observed aneuploid instability in the sample.
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

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

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

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. 2021. 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 and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test or the information contained in this report.

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

SELECT ABBREVIATIONS

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

MR Suite Version 4.1.0

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