FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chen, Hsin Lung	Lung adenocarcinoma	05 May 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1615095-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Lung adenocarcinoma
NAME Chen, Hsin Lung
DATE OF BIRTH 18 October 1991
SEX Male
MEDICAL RECORD # 22582098

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Spine
SPECIMEN ID S112-15519 A (PF23040)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 12 April 2023
SPECIMEN RECEIVED 25 April 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

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

EGFR exon 19 deletion (S752_I759del), amplification
ARAF amplification
FGFR1 amplification
BCL2L1 amplification - equivocal†
MCL1 amplification
NFKBIA amplification - equivocal†
NKX2-1 amplification - equivocal†
NSD3 (WHSC1L1) amplification
SRC amplification - equivocal†
TP53 R110P

7 Disease relevant genes with no reportable alterations: *ALK, BRAF, ERBB2, KRAS, MET, RET, ROS1*

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Afatinib** (p. 10), **Dacomitinib** (p. 11), **Erlotinib** (p. 12), **Gefitinib** (p. 13), **Osimertinib** (p. 14), **Cetuximab** (p. 15)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 16)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 2 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
***EGFR* -** exon 19 deletion (S752_I759del), amplification	Afatinib 1	Cetuximab 2A
	Dacomitinib 1	Panitumumab
	Erlotinib 1	
	Gefitinib 1	
	Osimertinib 1	
10 Trials see p. 18		
***ARAF* -** amplification	none	none
10 Trials see p. 16		

NCCN category

Electronically signed by Erik Williams, M.D. | 05 May 2023
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

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FGFR1 **-** amplification	none	none
10 Trials see p. 20		

NCCN category

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents 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 exhaustive. 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. 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.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[6]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2022).

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[16]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[16-18]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER

Tumor Mutational Burden

RESULT
2 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others);[22-23,26-28,32-39]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[40], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[41], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[42]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[43]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[44-45], several other large studies did find a strong association with increased TMB[46-49]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[50]. A meta-analysis of 19 studies of immune checkpoint inhibitor-treated NSCLC (n = 2,315 patients) demonstrated that high TMB predicted a significantly longer OS than low TMB (HR = 0.70), and within the high TMB group, immunotherapy was associated with an improved PFS (HR = 0.62, P<0.001), OS (HR = 0.67, P<0.001) and a higher response rate (OR = 2.35, P<0.001) compared to chemotherapy[51]. In contrast, a large study of Chinese patients with untreated lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[44]. Another study of patients with NSCLC treated with EGFR inhibitors or platinum doublet chemotherapy found elevated TMB to be correlated with poorer prognosis, as well as finding lower TMB in combination with PD-L1 negative status to be significantly associated with longer median survival in patients with lung adenocarcinoma[52]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[52-53].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[54-55] and cigarette smoke in lung cancer[32,56], treatment with temozolomide-based chemotherapy in glioma[57-58], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[59-63], and microsatellite instability (MSI)[59,62-63]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[22-23,26-28,32-39,64].

GENE
EGFR

ALTERATION
exon 19 deletion (S752_I759del), amplification

HGVS VARIANT
NM_005228.3: c.2254_2277del (p.S752_I759del)

VARIANT CHROMOSOMAL POSITION
chr7:55242483-55242507

VARIANT ALLELE FREQUENCY (% VAF)
48.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer (NSCLC), EGFR activating mutations may predict sensitivity to EGFR-TKIs, including erlotinib[65], gefitinib[66-69], afatinib[70-73], dacomitinib[74], and osimertinib[71,75]; however, the data for patients with other tumor types are limited[76-81]. EGFR amplification or expression in patients with non-small cell lung cancer may be associated with benefit from the anti-EGFR antibodies cetuximab[82-83] or necitumumab[84]. Although meta-analyses demonstrate that increased EGFR copy number is significantly associated with improved ORR, PFS, and OS on first-generation EGFR TKIs[85-88], 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[89-94]. 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)[89]. 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[95]. 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[96]. A Phase 1 study of amivantamab monotherapy or amivantamab in combination with lazertinib for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) has produced encouraging preliminary results for treatment-naive patients and patients who relapsed after treatment with osimertinib with and without chemotherapy, including osimertinib-relapsed patients with biomarkers indicating EGFR/MET-based osimertinib resistance[97-99]. A Phase 1/2 trial of MCLA-129, an EGFR/c-MET bispecific antibody, reported 1 PR in a patient with EGFR-mutated NSCLC who had received prior systemic treatment[100]01124-8). For patients with EGFR exon 18-mutated pretreated NSCLC, the updated results from the SUMMIT basket trial of neratinib reported an ORR of 34% (10/29) and a median PFS of 5.8 months, including ORRs of 30% (7/23) for TKI-pretreated patients, 50% (3/6) for TKI-naive patients, and 29% (2/7) for those with brain metastases[101]. In a Phase 1 trial, the HER3-targeted antibody patritumab deruxtecan elicited an ORR of 39% (22/57, 1 CR) and a median PFS of 8.2 months for patients with non-small cell lung cancer previously treated with an EGFR TKI, many of whom displayed TKI resistance alterations[102]. A Phase 1 trial evaluating the EGFR inhibitor AZD3759 reported a reduction in the volume of brain metastases in 40% (8/20) of patients with previously treated non-small cell lung cancer (NSCLC) harboring either the EGFR L858R alteration or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[103-104]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54% (69/127) for all evaluable patients and 44% (8/18, intracranial) for patients with brain metastases[105]. A Phase 1 trial evaluating the irreversible pan-HER inhibitor FCN-411 for NSCLC patients who had EGFR mutations and experienced disease progression on standard treatments reported an ORR of 15% with 10/67 patients achieving PR, and a DCR of 73% with 39 additional patients achieving SD[106]. OR was observed in a numerically higher proportion of patients with the EGFR T790M mutation than those without this mutation[106]. A Phase 1 study showed that the MET antibody-drug conjugate telisotuzumab vedotin (teliso-V) plus osimertinib yielded an ORR of 58% (11/19) for patients with EGFR-mutated, MET-overexpressing NSCLC who progressed on osimertinib, including ORRs of 56% (5/9) for patients with EGFR L858R mutation and 67% (6/9) for those with EGFR exon 19 deletion and no response for a patient with EGFR G719S mutation[107]. The Phase 3 AENEAS trial of first-line aumolertinib, a third-generation EGFR TKI, for patients with locally advanced or metastatic NSCLC harboring either the EGFR L858R alteration or EGFR exon 19 deletion reported significantly improved mPFS (19.3 months vs. 9.9 months) and similar ORR (74% vs. 72%) and DCR (93% vs. 97%) compared with gefitinib[108].

— Nontargeted Approaches —

Patients with EGFR-mutated non-squamous metastatic non-small cell lung cancer (NSCLC) who progressed on EGFR TKI have benefited from immune checkpoint inhibitors combined with antiangiogenic therapy and chemotherapy, particularly atezolizumab plus bevacizumab plus carboplatin and paclitaxel (OS HR=0.61 compared with bevacizumab/chemotherapy)[109-111] or sintilimab plus bevacizumab biosimilar IBI305 plus cisplatin and pemetrexed (PFS HR=0.46 compared with chemotherapy alone)[112].

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[48,113-114] and in 4% of lung squamous cell carcinomas[115]. Amplification of EGFR has been variously reported in 4-42% of non-small cell lung carcinoma (NSCLC) samples[114-118]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[116-121]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[122-123]. In patients with lung adenocarcinoma, EGFR gene amplification was a predictor of poor disease-free survival[124]. EGFR mutations have been reported to predict improved survival for patients with resected Stage 1-3 lung adenocarcinoma[125-126] or resected Stage 1 non-small cell lung cancer (NSCLC)[127]. For patients with advanced lung adenocarcinoma who did not undergo surgery, presence of EGFR mutations was associated with significantly longer survival than EGFR wildtype status (p=0.001); multivariate analyses identified TKI treatment and exon 19 deletion was significantly associated with reduced mortality (HR=0.678, p=0.002), whereas TKI treatment and exon 21 mutation was associated with increased mortality (HR=1.365, p=0.015)[128].

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[129]. EGFR exon 19 deletion mutations, such as seen here, have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib,

gefitinib[130-132], afatinib[133], osimertinib[134], and dacomitinib[74,135], although limited preclinical data suggest reduced sensitivity to lapatinib[136-137]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[117,138-139].

GENE
ARAF

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

ARAF activating mutations may predict sensitivity to pan-RAF and MEK inhibitors. In a preclinical study, cell transformation and hyperactivation of the MAPK pathway as a result of ARAF activation was reportedly inhibited by the MEK inhibitor trametinib and the pan-RAF inhibitor sorafenib[140]. Furthermore, 1 patient with Stage 4 lung adenocarcinoma whose tumor harbored the activating ARAF mutation S214C experienced a near-complete response and 5-year PFS upon sorafenib treatment[140].

FREQUENCY & PROGNOSIS

ARAF mutations have been reported in 1-3% of non-small cell lung carcinomas[47-48,114-115,141]. ARAF mutations have been associated with response to sorafenib in lung adenocarcinoma[140]. In a study of lung adenocarcinoma samples from six smokers and six nonsmokers, hypomethylation of ARAF has been observed in smokers but not in nonsmokers[142]. ARAF has been reported to be one of nine proteins associated with promoting cell viability of EGFR-mutated lung cancer cell lines[143]. Published data investigating the prognostic implications of ARAF alteration in lung cancer are limited (PubMed, Dec 2022).

FINDING SUMMARY

ARAF encodes a member of the RAF family of serine-threonine kinases that includes BRAF and CRAF and activates the MEK-ERK signaling cascade. Like CRAF, alteration of ARAF in cancer is thought to be rare compared to BRAF due to the requirement of activating phosphorylation of its negative-charge regulatory region[144]. ARAF overexpression and activating mutations have been reported to transform cultured cells and to hyperactivate the MEK-ERK MAPK pathway[140]. ARAF has been reported to be amplified in cancer[145] and may be biologically relevant in this context[146-147].

GENE
FGFR1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR1 may predict sensitivity to selective FGFR inhibitors including erdafitinib[148-150], pemigatinib[151], infigratinib[152-153], futibatinib[154-156], rogaratinib[157], Debio 1347[158-159], and derazantinib[160] or to multikinase inhibitors such as pazopanib[161] and ponatinib[162-164]. The activity and efficacy of selective FGFR inhibitors for FGFR1-amplified tumors has been modest, with limited responses reported in FGFR1-amplified lung squamous cell carcinoma (SCC) treated with infigratinib[165] or AZD4547[166], in FGFR1-amplifed uterine cancer treated with pemigatinib[151], and no responses reported among patients with FGFR1-amplified breast cancer treated with infigratinib[165] or pemigatinib[151]. Two case studies reported PRs in patients with FGFR1-amplified breast cancer treated with pazopanib[161].

FREQUENCY & PROGNOSIS

In the TCGA datasets, FGFR1 amplification was found in 3% of lung adenocarcinoma cases[114] and 17% of lung SCC cases[115]; FGFR1 mutation was observed in 1% of lung adenocarcinoma and lung SCC[114-115]. The prognostic significance of FGFR1 alteration in lung adenocarcinoma has not been extensively studied; however, 1 analysis of 345 non-small cell lung cancer (NSCLC) cases (48% adenocarcinoma, 39% squamous cell carcinoma [SCC], 7% large cell) suggested that high level amplification of FGFR1 was predictive of shorter survival[167]. The association between FGFR1 amplification and clinical parameters in lung SCC is not clear; some studies have suggested that FGFR1 amplification is associated with poor prognosis, whereas others have reported no association[168-171]. 1 study reported significant association between FGFR1 amplification and improved OS for patients assigned female (p=0.023), but not male (p=0.423), at birth[172].

FINDING SUMMARY

FGFR1 encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[173]. Amplification of FGFR1 has been correlated with protein expression[168,170] and may predict pathway activation and sensitivity to therapies targeting this pathway[174-175].

GENE
BCL2L1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Multiple investigational therapies that target BCL-2 family members, including ABT-737, navitoclax, pelcitoclax, A-1331852, and obatoclax, have been studied in preclinical studies or early-stage clinical trials[176-177]; clinical studies have been conducted in genomically unselected populations. Single-agent navitoclax has been evaluated in Phase 1 and Phase 2 studies where it demonstrated limited efficacy (ORR 2.6%, SD rate 20-23%); 2 patients achieved PRs, including a patient with small cell lung cancer who benefited for over 2 years[178-179]. Navitoclax has also been evaluated in combination with the EGFR TKI erlotinib, though no ORs were observed (27% SD rate, [3/11])[180]. In a Phase 1 trial for patients with advanced non-small cell lung cancer (NSCLC), the combination of pelcitoclax and EGFR TKI osimertinib resulted in an ORR of 15% (3/20)[181].

FREQUENCY & PROGNOSIS

BCL2L1 amplification has been observed in 1-6% of solid tumor samples, including colorectal (5%) and ovarian (6%) cancers[182-183]. Studies suggest that expression of BCL-XL may be associated with poor prognosis for patients with ovarian cancer[184], pleural mesothelioma[185], and colorectal cancer (CRC)[186]. Elevated BCL-XL levels protect cancer cells against apoptosis in multiple cancer types, and has been associated with chemotherapy resistance for patients with ovarian cancer[184,187] and resistance to radiation and targeted therapies in preclinical studies[185,188-192].

FINDING SUMMARY

BCL2L1 encodes BCL-XL, an anti-apoptotic member of the BCL-2 protein family that is frequently overexpressed in cancer[193-195]. In colorectal cancer (CRC), 20q gain has been associated with BCL-XL protein overexpression[196].

GENE
MCL1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to target MCL1 amplification, but MCL1 inhibitors including AMG 176, AMG 397, AZD5991, and S64315 (MIK665) are in early clinical development[197-200]. Limited preclinical data suggest that MCL1 expression alone may not be predictive of sensitivity to MCL1 inhibitors, but BH3 profiling may be a better predictor of MCL1 dependence[198,200-202]. Clinical and preclinical data indicate that increased MCL1 expression may be associated with resistance to BCL2-targeted agents such as venetoclax, navitoclax, or ABT-737[203-210]. In one study, amplification of the genomic locus containing MCL1 was acquired upon disease progression in patients with multiple myeloma treated with venetoclax[211]. Combined inhibition of MCL1 and BCL2 may be more effective[198-200,212-213]. Indirect approaches using therapeutic agents that reduce MCL1 expression are also being investigated[214]. Preclinical studies demonstrate that investigational cyclin-dependent kinase inhibitors targeting CDK9, such as dinaciclib, alvocidib, and voruciclib, suppress gene transcription, reduce MCL1 expression levels, and synergize with BCL2 inhibitors to induce apoptosis[215-222]. Preclinical studies in multiple types of cancer cells have also shown that the multikinase inhibitor sorafenib indirectly downregulates MCL1 and cooperates with BCL2-targeting agents[223-226], and a heavily pretreated patient with metastatic triple-negative breast cancer (TNBC) and MCL1 gene amplification responded to sorafenib in combination with several other therapies[227]. Preclinical studies of patient-derived tumor cells suggest that increased MCL1 levels may confer resistance to antitubulin therapies such as paclitaxel[228], and MCL1 amplification was reported to be more frequent in patients with TNBC and primary resistance to neoadjuvant chemotherapy[229].

FREQUENCY & PROGNOSIS

MCL1 amplification has been reported at the highest incidence in lung adenocarcinoma (16%)[114], breast invasive carcinoma (15%)[230], hepatocellular carcinoma (15%), and bladder urothelial carcinoma (13%)[231] and at lower frequencies in other solid tumor types (cBioPortal, 2023)[145,232]. MCL1 mutations have been reported in <1% of solid and hematologic cancers (COSMIC, 2023)[233]. For patients with non-small cell lung cancer (NSCLC), MCL1 amplification was significantly associated with shorter OS (HR=1.39)[234]; high MCL1 protein expression alone was not prognostic in NSCLC[235-237], whereas overexpression of both MCL1 and MYC was linked with poor survival[238]. High MCL1 expression has also been associated with poor prognosis in ovarian[239-240] and colorectal cancers (CRC)[241]. The prognostic significance of MCL1 expression in breast cancer is not clear[242-243].

FINDING SUMMARY

MCL1 (myeloid cell leukemia 1) encodes a member of the BCL2 family that regulates apoptosis[244]. Focal amplification of MCL1 has been reported in lung, breast, and other cancer types, and the survival of cells with MCL1 amplification is dependent on MCL1 expression[147]. In non-small cell lung cancer (NSCLC), MCL1 amplification was significantly associated with increased MCL1 mRNA expression[234]. Although several MCL1 phosphorylation site mutations have been characterized[245], cancer-associated MCL1 mutations have not been reported (PubMed, 2023).

GENE
NFKBIA

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that directly target NFKBIA amplification or expression.

FREQUENCY & PROGNOSIS

In the TCGA datasets, amplification of NFKBIA has been reported with the highest incidence in lung adenocarcinoma (11.7%)[114], esophageal carcinoma (3.8%), prostate adenocarcinoma (3.4%)[246], lung squamous cell carcinoma (2.8%)[115], and ovarian serous cystadenocarcinoma (2.6%) (cBioPortal, Jan 2023)[145,232]. Amplification or increased expression of NFKBIA in EGFR-mutant lung cancer has been reported to predict improved response to EGFR tyrosine kinase inhibitors[247-248]. Certain NFKBIA polymorphisms, which may affect IkBa expression levels, have been studied as risk factors for some cancer types, although the data are mixed and conflicting[249-251].

FINDING SUMMARY

NFKBIA encodes IkBa, an inhibitor of the NF-kappaB (NFkB)/REL complex. It has been reported to act as a tumor suppressor in Hodgkin's lymphoma[252-256] and in glioblastoma[249,257-258]. NFKBIA has been reported to be amplified in cancer[145] and may be biologically relevant in this context[146-147]. In contrast, truncating mutations that result in loss of the majority of the IkBa protein are predicted to be inactivating.

GENE
NKX2-1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies or trials that target tumors with TTF-1 amplification or overexpression.

FREQUENCY & PROGNOSIS

Amplification of NKX2-1 has been reported with the highest incidence in lung adenocarcinoma (14%)[114] and less frequently in lung squamous cell carcinomas (SCCs) (5%)[115]. NKX2-1 amplification has also been observed in other solid tumors, including prostate adenocarcinomas (6%)[246,259] and thyroid cancers (6%)[183,260]. NKX2-1 mutations have been infrequently reported in solid[183] or hematological malignancies[261-264]. Increased expression of NKX2-1 has been associated with favorable prognosis in lung adenocarcinoma, though this finding is not always significant[265-272]. Increased expression has been associated with a prolonged OS in gastric cancer[273]. Cytoplasmic TTF-1 expression has been reported as an adverse prognostic factor in breast carcinoma[274-275].

FINDING SUMMARY

NKX2-1 (also known as NK2 homeobox 1) encodes the thyroid transcription factor TTF-1[276]. Amplification of NKX2-1 results in overexpression of TTF-1[277]. TTF-1 has been observed to have tumor-promoting as well as anti-oncogenic roles[278-279].

GENE
NSD3 (WHSC1L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in NSD3.

FREQUENCY & PROGNOSIS

In TCGA datasets, NSD3 amplification has been most frequently observed in lung squamous cell carcinoma (17%), breast invasive carcinoma (13%), bladder urothelial carcinoma (8.8%), gastric carcinoma (8.3%), head and neck squamous cell carcinoma (7.0%), esophageal adenocarcinoma (6.0%), prostate adenocarcinoma (4.7%), and colorectal adenocarcinoma (4.6%) samples (Mar 2023)[145,232]. Amplification of at least 1 member of the NSD3-CHD8-BRD4 pathway has been associated with worse OS in ovarian high-grade serous carcinoma and endometrial cancer[280]. In endometrial cancers, amplification of this pathway was more frequent in endometrial serous and endometrioid serious-like carcinomas compared to low-grade endometrioid endometrial adenocarcinomas[280]. In breast cancers, high NSD3 (WHSC1L1) expression was associated with worse disease-free survival (DFS) and OS[281-282]. Published data investigating the prognostic implications of NSD3 alterations in other solid tumors are limited (PubMed, Mar 2023).

FINDING SUMMARY

NSD3, also known as WHSC1L1, encodes an enzyme that mediates histone methylation[283]. NSD3 has been shown to be amplified in various cancers[284-286].

GENE
SRC

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Dasatinib, a SRC and tyrosine kinase inhibitor, is approved for use in Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL). Bosutinib, which targets both ABL and SRC kinases, is approved to treat Ph+ CML with resistance or intolerance to prior therapy. Clinical trials of these agents and other SRC inhibitors are in progress in various cancer types[287-288].

— Nontargeted Approaches —

Overexpression of SRC in colorectal carcinoma may be associated with resistance to chemotherapy[289].

FREQUENCY & PROGNOSIS

In the TCGA datasets, SRC amplification was observed in 1.1% of lung squamous cell carcinomas (SCC)[115] and 1.7% of lung adenocarcinomas[114]. SRC activation has been shown to occur frequently in non-small cell lung cancer (NSCLC) tumors and cell lines, reported in 28-49% of lung tumors in the scientific literature[290-292]. Published data investigating the prognostic implications of SRC alterations in lung cancer are limited (PubMed, Nov 2022).

FINDING SUMMARY

The protein encoded by SRC belongs to a family of related non-receptor tyrosine kinases, members of which have been implicated in the growth and progression of a number of tumors, including breast, colon, and pancreatic cancer[293-295]. SRC has been reported to be amplified in cancer[145] and may be biologically relevant in this context[146-147].

GENE
TP53

ALTERATION
R110P

HGVS VARIANT
NM_000546.4: c.329G>C (p.R110P)

VARIANT CHROMOSOMAL POSITION
chr17:7579358

VARIANT ALLELE FREQUENCY (% VAF)
86.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[296-299] or p53 gene therapy such as SGT53[300-304]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[305]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[306]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[307]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[308]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[309]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[310]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[311]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[304]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[312]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[313].

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)[114-115,314-319], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, 2023)[48-49,114-115,145,232-233]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, 2023)[145,232]. 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[320]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[321].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[322]. Alterations such as seen here may disrupt TP53 function or expression[323-327].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[328]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[329-331], including sarcomas[332-333]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[334] to 1:20,000[333]. 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[335]. 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[336-341]. 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[336-337]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[342]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[340,343-344]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Afatinib

Assay findings association

EGFR
exon 19 deletion (S752_I759del), amplification

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[70,74,345-346] , whereas data for patients with other tumor types are limited[76-81,347] .

SUPPORTING DATA

Afatinib enabled 1 PR and 1 SD for 2 patients with EGFR-amplified NSCLC in a Phase 2 study[91]. In the first-line setting for patients who are EGFR TKI naive with non-small cell lung cancer (NSCLC) harboring common EGFR mutations (exon 19 or L858R alterations), afatinib has shown improved clinical benefit and responses as compared with chemotherapy in the Phase 3 LUX-Lung 3 and LUX-Lung 6 trials[70,345] and to gefitinib in the Phase 2b LUX-Lung 7 trial[348-349] ; these outcomes are supported in additional prospective or randomized Phase 2 trials[350-351] . Alteration-specific differences in OS response have also been reported in patients who are treatment naive, with increased OS observed in patients with EGFR exon 19 alterations between afatinib and comparator arms versus no significant OS differences for patients with L858R mutations in the same treatment settings[133,352] . In the second-line setting, patients with metastatic NSCLC and common EGFR mutations who progressed on prior chemotherapy experienced an ORR of 50% (30/60) from afatinib in a Phase 4 trial[353]. 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% for patients with common sensitizing EGFR mutations and an ORR of 24% for the entire cohort[354]. 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[355]. 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%[91,356-360] ; however, DCRs of more than 50% have been observed[91]. 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[361] or osimertinib[362], respectively. In the LUX-Lung 1 Phase 2b/3 trial for patients with advanced non-small cell lung cancer (NSCLC) who previously progressed on first-generation EGFR tyrosine kinase inhibitors, afatinib treatment resulted in longer median PFS (mPFS; 3.3 vs. 1.1 months, HR=0.38) but no significant difference in median OS (mOS; 10.8 vs. 12.0 months, HR=1.08) when compared with placebo[356]; similar results were observed in the single-arm LUX-Lung 4 trial in the same treatment setting[358]. The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer mOS (7.9 vs. 6.8 months, HR=0.81), significantly longer mPFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[363]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[364].

Dacomitinib

Assay findings association

EGFR
exon 19 deletion (S752_I759del), amplification

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[70,74,345-346] , whereas data for patients with other tumor types are limited[76-81,347] . Patients with untreated advanced NSCLC and EGFR exon 19 deletions achieved an ORR of 76%[135] and a median OS of 34.1 months with dacomitinib[74].

SUPPORTING DATA

A randomized Phase 3 trial for patients with non-small cell lung cancer (NSCLC) harboring activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS [mOS] of 34.1 vs. 26.8 months, HR=0.760; median PFS [mPFS] of 14.7 vs. 9.2 months, HR=0.59)[135,365] ; mOS was 34.1 to 36.7 months and ORR was 75% to 79%, depending on the dosing regimen[366]. A pooled subgroup analysis for patients with NSCLC harboring activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (mPFS of 14.6 vs. 9.6 months, HR=0.717; mOS of 26.6 vs. 23.2 months, HR=0.737)[367]. An analysis of dacomitinib in NSCLC comparing common activating EGFR alterations alone with co-occurring common and uncommon EGFR mutations showed no statistically significant difference in total ORR (33% vs. 40%, p=0.636) or DCR (77% vs. 73%, p=0.089); however, multivariate analysis revealed compound mutation status as an independent predictor of worse OS (HR=5.405)[368]. 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[369]. Phase 1/2 studies of dacomitinib for patients with advanced KRAS-wildtype non-small cell lung cancer (NSCLC) who had previously progressed on chemotherapy and erlotinib or gefitinib and were not selected for EGFR mutations reported ORRs of 4.6-17% (3/66-9/53), median PFS of 3-4 months, and median OS of 9-11 months[370-371] .

Erlotinib

Assay findings association

EGFR
exon 19 deletion (S752_I759del), 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. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[65,372-374] . 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[375-379] .

SUPPORTING DATA

In one study, median PFS (4.1 vs. 11.7 months, HR=9.7) and median OS (14.1 vs. 47.0 months, HR=10.2) were significantly shorter for patients with non-small cell lung cancer (NSCLC) harboring EGFR L747_A750>P (n=6) relative to those with deletions affecting EGFR E746_A750 (n=24) treated with first-line erlotinib[380]. For patients with EGFR-mutated non-small cell lung cancer (NSCLC), the Phase 3 EURTAC trial improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37), though OS was not prolonged (22.9 vs. 19.6 months, HR=0.92)[65,381] . This study and meta-analyses attribute the lack of OS benefit to the effectiveness of post-progression salvage therapy in the control arm[382]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[383]. Patients with EGFR-mutated NSCLC have experienced PFS benefit with the addition of bevacizumab to erlotinib in the first-line setting in Phase 3 trials, including the ARTEMIS-CTONG1509 trial for Chinese patients (17.9 vs. 11.2 months, HR=0.55)[384], the NEJ026 trial for Japanese patients (16.9 vs. 13.3 months, HR=0.605)[385-386] , and the international BEVERLY trial (15.4 vs. 9.7 months, HR=0.60)[387]; OS benefit has not been observed across these studies. In the maintenance setting, Phase 3 trials have reported significantly improved PFS with maintenance erlotinib following first-line platinum-based chemotherapy, with patients with EGFR mutations experiencing the largest benefit[372,388] . In the neoadjuvant setting, a Phase 2 trial reported a numerically improved ORR and significantly longer PFS with erlotinib compared with chemotherapy for patients with EGFR-mutated advanced NSCLC[373]. 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)[389]. A Phase 2 trial of cabozantinib plus erlotinib for patients with EGFR-mutated NSCLC who progressed on EGFR TKI reported an ORR of 11%, median PFS of 3.6 months, and median OS of 13.3 months; PFS and OS were similar for patients with or without T790M mutations[390].

Gefitinib

Assay findings association

EGFR
exon 19 deletion (S752_I759del), 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

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[374,391-396] , and responses have been reported for patients with EGFR-rearranged NSCLC[397-398] . 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[375-379] . Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant OS benefit from gefitinib compared with placebo (HR=0.21)[375,399] .

SUPPORTING DATA

Gefitinib achieved an ORR of 69.8% and OS of 19.2 months as first-line treatment for Caucasian patients with non-small cell lung cancer (NSCLC) and EGFR sensitizing mutations[66]. Phase 3 studies for Japanese patients[393,400] and East Asian patients[89,394] with EGFR-mutated NSCLC reported longer PFS but not longer OS on first-line gefitinib compared with cisplatin and docetaxel or carboplatin and paclitaxel. Retrospective analysis of East Asian patients receiving first-line gefitinib reported greatest PFS benefit among patients with EGFR exon 19 insertions or deletions and shortest PFS for those with exon 20 insertions (1.2 months)[401]. Two Phase 3 trials of the combination gefitinib plus pemetrexed and carboplatin compared with gefitinib alone for patients with advanced NSCLC harboring EGFR activating mutations reported significantly higher ORRs (75.3% and 84% vs. 62.5% and 67%), longer median PFS (16 and 20.9 months vs. 8 and 11.9 months), and longer median OS (50.9 months and not reached vs. 17 and 38.8 months) with combination treatment; however, combination treatment was associated with increased Grade 3 or higher adverse events[402-403] . In a Phase 1 study for treatment-naive patients with NSCLC, 63% (19/30) of patients experienced PR from the combination of gefitinib and the PD-L1 inhibitor durvalumab[404].

Osimertinib

Assay findings association

EGFR
exon 19 deletion (S752_I759del), 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 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[75,134,397,405-406] . 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[134].

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)[134,407] . In the Phase 3 ADAURA study, patients with early-stage (IB/II/IIIA) EGFR-mutated NSCLC experienced longer disease-free survival on osimertinib compared with placebo in the adjuvant setting (65.8 vs. 28.1 months, HR=0.27)[408]. 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[75]. A Phase 1b/2 study evaluating osimertinib in combination with the CD73 inhibitor oleclumab for patients with advanced EGFR-mutated, T790M-negative NSCLC reported an ORR of 19% (4/21), a DCR of 81%, and mPFS of 11 months (Kim et al., 2021 AACR Abstract CT163). A Phase 2 trial of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with untreated advanced non-small cell lung cancer (NSCLC) harboring EGFR del19 or L858R reported no difference in ORR (82% vs 86%) and median PFS (22.1 vs 20.2 months, HR 0.862 p=0.213)[409]. The Phase 2 BOOSTER study of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with advanced NSCLC with EGFR-sensitizing mutations (exon 19 del or L858R) and L790M at progression on prior EGFR TKI reported no difference in ORR (55% vs 55%), median OS (24.0 vs 24.3 months, HR 1.03 p=0.91), or median PFS (15.4 vs 12.3 months, HR 0.96 p=0.83), although improved PFS was observed for the combination in the subgroup of current or former smokers (16.5 vs 8.4, HR 0.52) while nonsmokers had no benefit (HR 1.47)[410]. 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[411].

Cetuximab

Assay findings association

EGFR
exon 19 deletion (S752_I759del), 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). 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[412].

SUPPORTING DATA

The Phase 3 FLEX study for patients with high EGFR expression in non-small cell lung cancer (NSCLC) demonstrated treatment with cetuximab plus chemotherapy resulted in longer OS compared with chemotherapy alone (12 vs. 9.6 months)[82]. A Phase 2 study of 31 patients with NSCLC found the addition of cetuximab to radiotherapy and chemotherapy produced an ORR of 67%; EGFR gene copy number was not predictive of efficacy outcome in this trial[413]. A Phase 3 study of 938 patients with progressive NSCLC after platinum-based therapy concluded the addition of cetuximab to chemotherapy was not recommended in this second-line setting[414]. Cetuximab is also being studied as part of a therapeutic regimen for patients with NSCLC with EGFR mutations who develop secondary resistance to erlotinib or gefitinib. A Phase 1b study combining afatinib and cetuximab for patients with either T790M-positive or T790M-negative tumors observed an overall ORR of 29% and comparable response rates in both groups (32% T790M positive vs. 25% T790M negative)[415]. A Phase 1 study evaluating the combination treatment of erlotinib and cetuximab for patients with NSCLC regardless of EGFR status, including squamous tumors, as well as those who had progressed on prior erlotinib treatment, reported PRs in 10% (2/20) of patients and SDs lasting at least 6 months in 15% (3/20) of patients[416]; in addition, a retrospective analysis of this trial identified a patient who had an exon 19 deletion and T790M who progressed rapidly on cetuximab and erlotinib[417].

Panitumumab

Assay findings association

EGFR
exon 19 deletion (S752_I759del), 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[412].

SUPPORTING DATA

In a Phase 2 trial for patients with advanced non-small cell lung cancer (NSCLC), the addition of panitumumab to paclitaxel/carboplatin did not result in improved clinical benefit[418]; a subsequent Phase 2 study investigating the addition of panitumumab to pemetrexed/cisplatin reported no benefit for patients with wildtype KRAS lung adenocarcinoma[419]. The combination of afatinib and panitumumab has been explored for 2 patients with EGFR T790M NSCLC, with 1 PR reported[420].

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 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. 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 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. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
ARAF

ALTERATION
amplification

RATIONALE
ARAF activating mutations may lead to increased RAF activity and subsequent activation of the MEK pathway and may predict sensitivity to therapies targeting these pathways.

NCT03337698

PHASE 1/2

A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)

TARGETS
PD-L1, MEK, CEA, CXCR4, EZH2, MDM2, ADORA2A

LOCATIONS: Taipei City (Taiwan), Seoul (Korea, Republic of), Blacktown (Australia), Haifa (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Newcastle upon Tyne (United Kingdom), Dijon (France), London (United Kingdom), Sutton (United Kingdom)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04985604

PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs, NRAS

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

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

NCT03600701

PHASE 2

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

TARGETS
PD-L1, MEK

LOCATIONS: Michigan, Oklahoma, New Hampshire, Ohio, Pennsylvania, New York, District of Columbia, Virginia, North Carolina

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

GENE
EGFR

ALTERATION
exon 19 deletion (S752_I759del), amplification

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.

NCT05338970

PHASE 3

HERTHENA-Lung02: A Study of Patritumab Deruxtecan Versus Platinum-based Chemotherapy in Metastatic or Locally Advanced EGFRm NSCLC After Failure of EGFR TKI Therapy

TARGETS
ERBB3

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung City (Taiwan), Shantou (China), Hangzhou (China), Hong Kong (Hong Kong), Nanjing (China), Guangzhou (China)

NCT05120349

PHASE 3

A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection

TARGETS
EGFR

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Fuzhou (China), Tainan (Taiwan), Shanghai (China), Suzhou (China), Shenzhen (China), Nanjing (China)

NCT04988295

PHASE 3

A Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With Epidermal Growth Factor Receptor (EGFR)-Mutated Locally Advanced or Metastatic Non- Small Cell Lung Cancer After Osimertinib Failure

TARGETS
MET, EGFR

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Changhua (Taiwan), New Taipei City (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Linhai (China), Hangzhou (China), Shanghai (China), Hang Zhou (China)

NCT05215548

PHASE 2

Primary Tumor Resection With EGFR TKI for Stage IV NSCLC

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Taipei (Taiwan)

NCT05442060

PHASE 2

To Evaluate OBI-833/OBI-821 in Combination With First-Line Erlotinib in Patients With EGFR-Mutated, Globo H-Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

TARGETS
EGFR

LOCATIONS: Taipei (Taiwan)

NCT03974022

PHASE 1/2

Assessing an Oral EGFR Inhibitor, DZD9008 in Patients Who Have Advanced Non-small Cell Lung Cancer With EGFR or HER2 Mutation (WU-KONG1)

TARGETS
ERBB2, EGFR

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Liuying (Taiwan), Tainan (Taiwan), Cheonju (Korea, Republic of), Suwon (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang (Korea, Republic of)

NCT03114319

PHASE 1

Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors

TARGETS
SHP2, EGFR

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Kobe-shi (Japan), Singapore (Singapore), Amsterdam (Netherlands), Leiden (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Hospitalet de LLobregat (Spain), Madrid (Spain)

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: Taipei City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Hang Zhou (China), Shanghai (China), Guangzhou (China), Changsha (China), Wuhan (China), Jinan (China)

NCT04862780

PHASE 1/2

Study Targeting EGFR Resistance Mechanisms in NSCLC

TARGETS
EGFR

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Yokohama-shi (Japan), Chuo Ku (Japan), Kashiwa (Japan), Singapore (Singapore), Amsterdam (Netherlands), Sutton (United Kingdom), Villejuif (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: Taipei City (Taiwan), Tainan (Taiwan), Suwon (Korea, Republic of), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), Nijmegen (Netherlands), Marseille CEDEX 05 (France), California

GENE
FGFR1

ALTERATION
amplification

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR1.

NCT05024214

PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT05014828

PHASE 2

To Evaluate the Efficacy and Safety of Tislelizumab in Combination With Lenvatinib in Patients With Selected Solid Tumors

TARGETS
PD-1, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Hangzhou (China), Nanchang (China), Nanjing (China), Hefei (China), Changsha (China), Wuhan (China), Nanning (China), Chongqing (China), Beijing (China), Harbin (China)

NCT05098847

PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Shanghai (China)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Shanghai (China), Seoul (Korea, Republic of), Chengdu (China), Changchun (China), Brisbane (Australia), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel)

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, CTLA-4

LOCATIONS: Daejeon (Korea, Republic of), Suwon-si (Korea, Republic of), Seoul (Korea, Republic of), North Carolina

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT05003037

PHASE 2

Surufatinib Combined With Toripalimab and Chemotherapy in the Treatment of Non-Small Cell Lung Cancer

TARGETS
FGFR1, CSF1R, VEGFRs, PD-1

LOCATIONS: Guangzhou (China)

NCT05077384

PHASE 1/2

Open-label Study of Surufatinib in Japanese Patients

TARGETS
FGFR1, CSF1R, VEGFRs

LOCATIONS: Sendai (Japan), Fukuoka (Japan), Kagawa (Japan), Osaka (Japan), Nagoya (Japan), Tokyo (Japan), Yokohama (Japan), Mitaka (Japan), Kashiwa-shi (Japan), Sapporo (Japan)

NCT04008797

PHASE 1

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

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

LOCATIONS: Kurume (Japan), Matsuyama (Japan), Seodaemun (Korea, Republic of), Osakasayama (Japan), Nagoya (Japan), Kawasaki (Japan), Chuo-Ku (Japan), Koto-ku (Japan), Chiba (Japan), Kashiwa (Japan)

NCT04565275

PHASE 1/2

A Study of ICP-192 in Patients With Advanced Solid Tumors

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

LOCATIONS: Benowa (Australia), Westmead (Australia), Macquarie Park (Australia), St Leonards (Australia), Melbourne (Australia), Clayton (Australia), Frankston (Australia), California, Colorado, Minnesota

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.

AKT3
amplification

APC
NM_000038.4: c.3374T>C
(p.V1125A)
chr5:112174665

AR
NM_000044.2: c.528C>A
(p.S176R)
chrX:66765516

ARFRP1
amplification

ASXL1
amplification

AURKA
amplification

AXIN1
rearrangement and
rearrangement

BRCA2
NM_000059.3: c.9097A>C
(p.T3033P)
chr13:32954030

BTK
amplification

CARD11
amplification

CCND3
amplification

CDKN1A
amplification

CREBBP
amplification

DAXX
amplification

DDR1
amplification

DDR2
NM_006182.2: c.1308G>A
(p.M436I)
chr1:162740106

ERCC4
amplification

FH
amplification

GNAS
amplification

H3-3A (H3F3A)
amplification

IKZF1
amplification

IRF4
amplification

IRS2
NM_003749.2: c.3806A>C
(p.Q1269P)
chr13:110434595

KDM5C
amplification

KDM6A
amplification

MYCL (MYCL1)
NM_001033082.2: c.1022T>A
(p.L341Q)
chr1:40363207

NFE2L2
NM_006164.4: c.1660A>C
(p.K554Q)
chr2:178095671

NKX2-1
NM_003317.3: c.964G>A
(p.G322S)
chr14:36986635

NOTCH3
NM_000435.2: c.499C>T
(p.P167S)
chr19:15302951

PALB2
amplification

PARP1
amplification

PARP3
NM_005485.4: c.1223G>A
(p.R408H)
chr3:51980306

PIM1
amplification

PMS2
amplification

RAC1
amplification

RBM10
amplification

ROS1
NM_002944.2: c.4058A>C
(p.Y1353S)
chr6:117677875

SMO
NM_005631.4: c.1618G>A
(p.A540T)
chr7:128850355

SOX2
NM_003106.2: c.578A>T
(p.Q193L)
chr3:181430726

TSC2
amplification

VEGFA
amplification

ZNF217
amplification

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. 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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Homologous Recombination status
Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne 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: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx 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 solid malignant neoplasms.

TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

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. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. 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.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

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

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

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. 2023. 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.

Limitations

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

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 >10%, 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, CBL, 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.

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 CDx.

TREATMENT DECISIONS ARE 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 or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.8.0

The median exon coverage for this sample is 836x

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