FOUNDATIONONE®LIQUID CDx

PATIENT
Huang, Chien-Cheng

TUMOR TYPE
Lung adenocarcinoma
COUNTRY CODE
TW

REPORT DATE
23 May 2022
ORDERED TEST #
ORD-1363381-01

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

PATIENT
DISEASE Lung adenocarcinoma
NAME Huang, Chien-Cheng
DATE OF BIRTH 14 March 1958
SEX Male
MEDICAL RECORD # 8359453

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

SPECIMEN
SPECIMEN ID C.C.H. 03/14/1958
SPECIMEN TYPE Blood
DATE OF COLLECTION 10 May 2022
SPECIMEN RECEIVED 16 May 2022

Biomarker Findings

Blood Tumor Mutational Burden - 3 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

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

ERBB2 V659E
STK11 L105*
KEAP1 V79fs*48
SMARCA4 I1039fs*43
TNFAIP3 D100fs*23

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Ado-trastuzumab emtansine** (p. 10), **Fam-trastuzumab deruxtecan** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
Tumor Fraction - Elevated Tumor Fraction Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).**

GENOMIC FINDINGS		VAF %
ERBB2 -	V659E	0.61%

10 Trials see p. 13

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)	
Afatinib	Ado-trastuzumab emtansine	2A
Dacomitinib	Fam-trastuzumab deruxtecan	2A
	Neratinib	
	Trastuzumab	
	Trastuzumab + Pertuzumab	

☐ *NCCN category*

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GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
STK11 - L105*	0.54%	None	None
2 Trials see p. 15			

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

Variant Allele Frequency is not applicable for copy number alterations.

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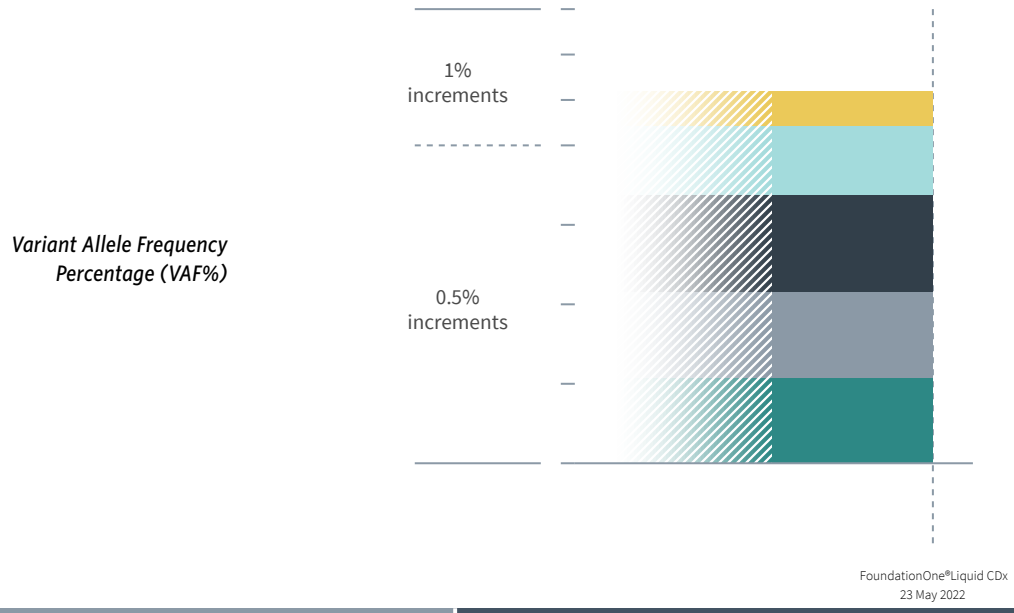

HISTORIC PATIENT FINDINGS		ORD-1363381-01 VAF%
Blood Tumor Mutational Burden		3 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
ERBB2	V659E	0.61%
STK11	L105*	0.54%
KEAP1	V79fs*48	0.76%
SMARCA4	I1039fs*43	0.75%
TNFAIP3	D100fs*23	0.54%

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

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

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

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

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BIOMARKER

Blood Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)[3]. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic non-small cell lung cancer (NSCLC) reported that bTMB ≥7 Muts/Mb was associated with shorter PFS (2.8 vs. 4.2 months) and OS (7.4 vs. 11.9 months) compared with bTMB <7 Muts/Mb for patients treated with docetaxel[5]. In one study of advanced NSCLC in China, bTMB ≥6 Muts/Mb was associated with decreased PFS (10 vs. 18 months) and OS (11 vs. 25 months) compared with bTMB <6 Muts/Mb for patients treated with platinum-based chemotherapy[6]. A meta-analysis of 19 studies of immune checkpoint inhibitor-treated NSCLC (n = 2,315 patients) demonstrated that high TMB predicted a significantly longer OS than low TMB (HR = 0.70), and within the high TMB group, immunotherapy was associated with an improved PFS (HR = 0.62, P<0.001), OS (HR = 0.67, P<0.001) and a higher response rate (OR = 2.35, P<0.001) compared to chemotherapy[7]. In contrast, a large study of Chinese patients with untreated lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[8]. Another study of patients with NSCLC treated with EGFR inhibitors or platinum doublet chemotherapy found elevated TMB to be correlated with poorer prognosis, as well as finding lower TMB in combination with PD-L1 negative status to be significantly associated with longer median survival in patients with lung adenocarcinoma[9]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[9-10].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[11-12] and cigarette smoke in lung cancer[13-14], treatment with temozolomide-based chemotherapy in glioma[15-16], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[17-21], and microsatellite instability (MSI)[17,20-21]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[22-27].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[28]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[29], Ewing sarcoma and osteosarcoma[30], prostate cancer[25], breast cancer[31], leiomyosarcoma[32], esophageal cancer[33], colorectal cancer[34], and gastrointestinal cancer[35].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[36], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[37-38].

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GENE
ERBB2

ALTERATION
V659E

TRANSCRIPT ID
NM_004448

CODING SEQUENCE EFFECT
1976_1977TT>AA

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[39-44], pertuzumab in combination with trastuzumab[41,45-47], and zanidatamab (ZW25)[48], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[49] and fam-trastuzumab deruxtecan[50], HER2 kinase inhibitors such as tucatinib[51-54], and dual EGFR/HER2 kinase inhibitors such as lapatinib[55-63], afatinib[44,64-73], neratinib[74-77], dacomitinib[78], and pyrotinib[79-80] . In Phase 2 clinical studies, patients with non-small cell lung cancer (NSCLC) harboring ERBB2 missense mutations have benefited from HER2-targeted therapies, including fam-trastuzumab deruxtecan (31% PR, 4/13)[81], ado-trastuzumab emtansine (29% PR, 2/7)[82], and pyrotinib (27% PR, 3/11)[83].

FREQUENCY & PROGNOSIS

ERBB2 mutations have been reported in 2.2–4.2% of lung adenocarcinomas and lung squamous cell carcinomas across several genomic studies[84-89].

HER2 overexpression has been documented in 11-32% of NSCLC cases, and is generally reported more frequently in non-squamous histologies[90-91]. Expression of HER2 has generally been associated with poor prognosis in NSCLC in several studies[92-96].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. ERBB2 V659E has been demonstrated to be activating and oncogenic[58,97-99] and is associated with sensitivity to afatinib[100-101] and lapatinib[58]. The compound ERBB2 mutation V659_G660>ER has also been associated with a durable PR to afatinib in a lung adenocarcinoma case[100].

GENE
STK11

ALTERATION
L105*

TRANSCRIPT ID
NM_000455

CODING SEQUENCE EFFECT
314T>G

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations[102-106]. Case studies have reported PRs for 2 patients with STK11-mutated pancreatic cancer following treatment with the mTOR inhibitor everolimus[107], with 1 PR observed in a PJS patient for 9 months until progression[107]. However, retrospective analysis of a Phase 2 trial for patients with endometrial carcinoma found LKB1 (STK11) protein levels were not significantly correlated with response to everolimus treatment[108]. In one preclinical study, STK11 loss was associated with sensitivity to combination treatment including an SRC inhibitor[109]; however, the clinical relevance of these findings has not been established.

— Potential Resistance —

STK11 alteration is associated with poorer response to immune checkpoint inhibitors for patients with non-small cell lung cancer (NSCLC), including those with tumors harboring co-occurring KRAS or KEAP1 mutations. Following anti-PD-1-based regimens, retrospective analyses have reported shorter OS for patients with KRAS and STK11 co-mutated tumors than for patients with wild-type STK11 (6.4 vs. 16.1 months, HR=1.99)[110], as well as markedly fewer objective responses for patients with KRAS/STK11 co-mutated versus KRAS/TP53 co-mutated tumors in the CheckMate-057, CheckMate-012, and GEMINI trials (0% vs. 53-78%%)[110-111], although a case study reported ongoing response for 1 patient with KRAS/STK11 co-mutations treated with nivolumab and ipilimumab[112]. Patients with NSCLC and concurrent mutation of STK11 and KEAP1 (n=39) who received treatment with a PD-L1 inhibitor experienced significantly shorter PFS (1.6 vs. 2.5 months; HR=1.5) and OS (4 vs. 11 months; HR=1.9) compared with patients with STK11- and KEAP1-wild-type tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 Muts/Mb)[113]. However, exploratory analyses of patients with NSCLC treated in the first-line setting with pembrolizumab showed trends towards improved ORR and OS irrespective of STK11 or KEAP1 mutation status, though this was not demonstrated to be statistically significant[114-115] . In the absence of co-mutations, reduced clinical benefit has also been reported for patients with NSCLC harboring STK11 mutations compared with wild-type STK11 and either anti-PD-L1[116-117] or anti-PD-1 therapy[118].

FREQUENCY & PROGNOSIS

Several clinical studies have found STK11 mutation to be common in non-small cell lung cancer (NSCLC) (15-35%), with alterations more prevalent in lung adenocarcinomas (13-34%) than in lung squamous cell carcinoma (2-19%)[87,89,103,119-122]. In the TCGA datasets, STK11 homozygous deletion was observed in 1% of lung adenocarcinoma cases[86] and was not observed in any of 178 lung squamous cell carcinoma cases[89]. STK11 mutations in NSCLC often co-occur with activating KRAS mutations[121-122]. In transgenic mouse models, animals expressing mutant KRAS developed lung adenocarcinomas, whereas the KRAS-mutant/LKB1-deficient mice developed an expanded histological spectrum of tumors that included large cell and squamous cell carcinomas[103]. Strongly decreased or absent expression of LKB1 correlated with inferior outcome in patients with NSCLC treated with bevacizumab-containing chemotherapy; expression of LKB1 was not prognostic in patients treated with chemotherapy without bevacizumab[123].

FINDING SUMMARY

The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels[102]. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis[109,124]. Alterations such as seen here may disrupt STK11 function or expression[125-136].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation[137]. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly[137-139]. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers[137-139], and individuals with this syndrome have a 30-50% risk of developing breast cancer[137,139]. Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.

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GENE
KEAP1

ALTERATION
V79fs*48

TRANSCRIPT ID
NM_012289

CODING SEQUENCE EFFECT
234_235insT

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A study of patients with localized non-small cell lung cancer (NSCLC) identified pathogenic KEAP1 and NFE2L2 mutations as predictors of local recurrence following radiotherapy but not surgery; limited preclinical data also showed that treatment with a glutaminase inhibitor sensitized KEAP1-mutated NSCLC cells to radiation[140]. In other preclinical studies, treatment with AKT inhibitors sensitized lung cancer cells harboring KEAP1 or NFE2L2 mutations to both chemotherapy and radiation therapy[141-142]. Mixed clinical data have been reported for the association between KEAP1 mutations and the response to immunotherapy. A pan-cancer study of immunotherapy showed that patients with KEAP1 mutations had shorter OS (10 vs. 20 months) than those without[143]. However, another study across solid tumors showed that KEAP1 mutations were associated with higher tumor mutational burden (TMB) and PD-L1 expression, as well as improved survival outcomes with immunotherapy compared with other treatments (20.0 vs. 11.5 months)[144]. For patients with non-small cell lung cancer (NSCLC), a study of PD-L1 inhibitors showed that patients with concurrent mutations of STK11 and KEAP1 (n=39) experienced significantly shorter PFS (1.6 vs. 2.5 months, HR=1.5) and OS (4 vs. 11 months, HR=1.9) compared with patients with STK11- and KEAP1-wildtype tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 Muts/Mb)[113]. Retrospective analyses of patients with NSCLC who received immunotherapy reported reduced OS (p=0.040) for patients harboring KEAP1- or NFE2L2-mutated tumors[145] or STK11- or KEAP1-mutated tumors (p <0.001)[146] compared with those without. Studies of immune checkpoint inhibitors for patients with lung adenocarcinoma showed that coexisting mutations between KEAP1, PBRM1, SMARCA4, STK11, and KRAS were associated with worse OS[147]. An exploratory analysis of a subset of patients with PD-L1-positive NSCLC treated in the first-line setting with pembrolizumab showed similar ORR, PFS, and OS when comparing patients with STK11 or KEAP1 mutations and those without[114]. In addition, preclinical data suggest that KEAP1 inactivation increases tumor demand for glutamine and increases tumor sensitivity to glutaminase inhibitors like telaglenastat[148-150]. Limited clinical data suggest that KEAP1 mutations may predict improved clinical benefit from combinations of glutaminase inhibitors and anti-PD-1 inhibitors[151]; a Phase 1/2 study of the glutaminase inhibitor telaglenastat (CB-839) plus nivolumab to treat advanced NSCLC reported better clinical benefit rates and median PFS for patients with KEAP1 mutations (75% [3/4] vs. 15% [2/13], 6.4 vs. 3.7 months), KRAS mutations (38% [3/8] vs. 20% [2/10], 4.5 vs. 3.7 months), or KEAP1 and KRAS concurrent mutations (100% [2/2] vs. 13% [1/8], 7.2 vs. 3.7 months) compared with patients without these mutations[151]. The KEAP1 mutation has also been identified as a potential biomarker for sensitivity to combined AKT and TXNRD1 inhibition in lung cancer[152].

FREQUENCY & PROGNOSIS

Somatic mutation of KEAP1 occurs in a range of solid tumors, including gastric, hepatocellular, colorectal, and lung cancers[153]. KEAP1 mutations are rare in hematological malignancies, occurring in fewer than 1% of samples analyzed (COSMIC, 2022)[154]. In a retrospective analysis of the pan-solid MSKCC dataset, KEAP1 mutation correlated with reduced OS (13.28 vs. 26.53 months)[144]. For patients with non-small cell lung cancer (NSCLC), mutation of KEAP1 and/or NFE2L2 also correlated with reduced median OS (11.51 vs. 22.32 months)[144]. In another study, for NSCLC treated with frontline chemotherapy, multivariate analysis showed that KEAP1 and/or NFE2L2 mutations significantly associated with reduced survival for patients with adenocarcinoma (PFS HR=2.34, OS HR=1.96) but not for patients with squamous cell carcinoma[155].

FINDING SUMMARY

KEAP1 encodes a substrate adaptor protein that regulates the cellular response to oxidative stress by providing substrate specificity for a CUL3-dependent ubiquitin ligase[156]. KEAP1 exerts anti-tumor effects through negative regulation of NRF2, a transcription factor encoded by NFE2L2[157-159]; KEAP1 inactivation promotes cancer progression through NRF2-mediated chemoresistance and cell growth[158-159].

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GENE
SMARCA4

ALTERATION
I1039fs*43

TRANSCRIPT ID
NM_003072

CODING SEQUENCE EFFECT
3114_3115insC

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical[160] and preclinical[161-167] data suggest that patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) harboring SMARCA4 loss or inactivation may benefit from treatment with EZH2 inhibitors, including tazemetostat. In addition, preclinical data have demonstrated that SMARCA4-deficient non-small cell lung cancer (NSCLC) and SCCOHT patient-derived xenografts and cell lines are highly sensitive to CDK4/6 inhibition through a synthetic lethal mechanism of reduced cyclin D1 expression[168-169]. Notably, similar drug sensitivity was detected in SMARCA4-deficient lung and ovarian tumors, thereby suggesting that SMARCA4-deficient tumors are likely to be sensitive to CDK4/6 inhibition regardless of tissue of origin[168-169].

— Nontargeted Approaches —

Downregulation of BRG1 and BRM was reported to enhance cellular sensitivity to cisplatin in lung and head and neck cancer cells[170]. In vitro studies have shown that SCCOHT cell lines are sensitive to treatment with epothilone B, methotrexate, and topotecan, compared to treatment with other chemotherapies such as platinum-containing compounds; similar sensitivity was not observed for treatment with ixabepilone, a compound closely related to epothilone B[171].

FREQUENCY & PROGNOSIS

In the TCGA datasets, SMARCA4 mutations have been reported in 6% of lung adenocarcinomas[86] and in 5% of lung squamous cell carcinomas[89]. Loss of BRG1 protein expression has been observed in 10-15% of non-small cell lung cancer (NSCLC) cases in the scientific literature[172-174]. Loss of expression of BRG1 and BRM, another catalytic subunit in SWI/SNF chromatin remodeling complexes, has been correlated with poor prognosis in patients with NSCLC[172-173,175-176].

FINDING SUMMARY

SMARCA4 encodes the protein BRG1, an ATP-dependent helicase that regulates gene transcription through chromatin remodeling[177]. SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor[178]. Alterations such as seen here may disrupt SMARCA4 function or expression[179-183].

GENE
TNFAIP3

ALTERATION
D100fs*23

TRANSCRIPT ID
NM_006290

CODING SEQUENCE EFFECT
300delC

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that address the loss of TNFAIP3. A20 has multiple functions and is subject to a wide range of genomic lesions, thereby making it challenging to develop a unified therapeutic approach. Potential avenues targeting dysregulation of ubiquitination pathways include anti-CD20 therapies, such as rituximab, and proteasome inhibitors, such as bortezomib[184]. RNAi-mediated downregulation of TNFAIP3 has been reported to sensitize multiple myeloma cells to bortezomib[185].

FREQUENCY & PROGNOSIS

In the COSMIC dataset, TNFAIP3 mutations have been reported in 3.5% of prostate, 3.1% of endometrial, 2.8% of skin, 2.7% of gastric, and 2.4% of large intestine cancers (Jan 2022)[154]. Overexpression of TNFAIP3 has been associated with aggressive high-grade ER-/PR-negative breast tumors[186], resistance to TNF-alpha and TRAIL-induced apoptosis in glioblastoma[187-188] and to chemotherapy in acute lymphoblastic leukemia[189], and poor prognosis in adrenocortical carcinoma[190]. Loss of heterozygosity in the genomic region including TNFAIP3 has been found in 16.8% (25/149) of colorectal adenocarcinomas, and significantly decreased TNFAIP3 mRNA expression has been observed in colorectal cancer (CRC) tumors compared with adjacent non-neoplastic mucosa[191]. Reduced A20 expression has been suggested as a marker of poor prognosis in CRC[192].

FINDING SUMMARY

TNFAIP3 encodes tumor necrosis factor alpha-induced protein 3, also known as A20, a regulator of NF-kB signaling and apoptosis[193] that has both ubiquitin ligase and deubiquitinase activities[194-195] and whose loss or inactivation may be tumorigenic[196]. TNFAIP3 is frequently deleted or mutated in lymphoma, where it functions as a tumor suppressor[196], but its expression and function are context dependent in solid tumors[193,197-200], leukemia[189,201-202], and multiple myeloma[203-204]. TNFAIP3 mutations that disrupt the A20p37 chain (amino acids 371–790), which mediates ubiquitin ligase activity and interaction with the cIAP1/TRAF2 complex[194,205], are predicted to be inactivating. In T-cells, cleavage of A20 codon R439 by MALT1 has been shown to upregulate NFkB signaling; R439A has been shown to block MALT1-mediated NF-kB activation[206]; however, the function of R439 mutations outside of the context of T-cell lymphoma has not been reported.

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Afatinib

Assay findings association

ERBB2
V659E

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

Clinical and preclinical data support sensitivity of multiple activating mutations in ERBB2, including A775_G776insYVMA and P780_Y781insGSP, to afatinib[69-73,207-210] . Studies have reported DCRs of 54-70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[69-73] . Clinical responses to afatinib have been reported in several patients with lung adenocarcinoma harboring ERBB2 V659E[100-101] .

SUPPORTING DATA

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[211-217] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[44,66-70,72-73,207,218-220] . 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[216]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[221].

Dacomitinib

Assay findings association

ERBB2
V659E

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

Prospective early-phase single-arm clinical trials report anti-tumor activity of dacomitinib in advanced solid tumors with ERBB2 activating mutations[78,222] , ERBB2 amplification[223-224] , or HER2 overexpression[225].

SUPPORTING DATA

In a Phase 2 study, 3/26 (12%) of patients with ERBB2 exon 20 mutations experienced PRs to dacomitinib treatment; the median PFS was 3 months and median OS was 9 months in this cohort[78]. In ERBB2-amplified NSCLC, response rates of 0/4 (0%)[78] to 1/3 (33%)[224] have been reported, with disease control (PR or SD) achieved in 4/9 (44%) patients total[78,222,224] . 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[226]. 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)[224]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[227].

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Ado-trastuzumab emtansine

Assay findings association

ERBB2
V659E

AREAS OF THERAPEUTIC USE

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy as well as patients with HER2+ early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1[49,228-243] .

SUPPORTING DATA

In a Phase 2 basket trial of T-DM1, patients with ERBB2-mutated and/or -amplified non-small cell lung cancer (NSCLC) achieved an ORR of 51% (25/49) and a median PFS of 5 months. The ERBB2-amplified cohort had an ORR of 55% (6/11), while the ERBB2-mutated cohort had an ORR of 50% (5/10). A subset of patients with tumors harboring both an ERBB2 mutation and amplification had an ORR of 50% (5/10)[230]. Another Phase 2 trial of T-DM1 in chemotherapy-refractory ERBB2-positive NSCLC reported an ORR of 6.7% and a median PFS of 2.0 months; patients with ERBB2 expression experienced an ORR of 0% (0/8) and a DCR of 38% (3/8), whereas patients with ERBB2 exon 20 insertion mutations experienced an ORR of 14% (1/7) and DCR of 71% (5/7)[231]. A patient with ERBB2-amplified and A775_G776insYVMA-mutated NSCLC experienced disease progression on 2 prior lines of chemotherapy but experienced a rapid and durable response to T-DM1[219,244] .

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
V659E

AREAS OF THERAPEUTIC USE

Fam-trastuzumab deruxtecan is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface and delivers the cytotoxic payload DXd, which inhibits DNA topoisomerase I to induce DNA damage. Fam-trastuzumab deruxtecan is FDA approved to treat patients with HER2-positive breast cancer and gastric or gastroesophageal junction adenocarcinoma who have received prior HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer (NSCLC)[81,245] , ERBB2 missense or exon 20 insertion mutations may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

The multi-cohort Phase 2 DESTINY-Lung01 study of single-agent fam-trastuzumab deruxtecan for patients with ERBB2-altered non-small cell lung cancer (NSCLC) reported clinical benefit for both the ERBB2-mutated[81] and ERBB2-overexpressing cohorts[246]. In the ERBB2-mutated cohort, predominantly comprised of patients with NSCLC harboring exon 20 insertions, the ORR was 55% (50/91) with a median duration of response of 9.3 months and the median PFS (mPFS) and OS were 8.2 and 17.8 months, respectively[81]. In the ERBB2-overexpressing cohort, the ORR and DCR were 25% (12/49) and 69% (34/49), respectively[246]. A Phase 1 basket study evaluating fam-trastuzumab deruxtecan for patients with ERBB2-expressing or -mutated NSCLC elicited an ORR of 56% (10/18) and a DCR of 83% (15/18), with an mPFS of 11 months[245]. In this study, the ORR was 73% (8/11) for patients with ERBB2-mutated NSCLC, with 6 responses reported for patients with ERBB2 exon 20 insertions[245]. A patient with lung cancer harboring both ERBB2 amplification and the S310F mutation who had progressed on ado-trastuzumab emtansine after 4 months was treated with fam-trastuzumab deruxtecan and exhibited a PR that lasted for 1 year[230].

Neratinib

Assay findings association

ERBB2
V659E

AREAS OF THERAPEUTIC USE

Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the extended adjuvant treatment of early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab. Neratinib is also approved in combination with capecitabine to treat patients with advanced or metastatic HER2+ breast cancer who have been previously treated with 2 or more anti-HER2 regimens. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[74-77,247-249] and preclinical[250-254] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

In the Phase 2 SUMMIT trial of neratinib in patients with ERBB2 or ERBB3 mutations, the ORR was 3.8% (1/26) and the median PFS was 5.5 months for patients with NSCLC, most of whom harbored ERBB2 exon 20 insertions; PR was observed in one patient with L755S mutation[76]. A Phase 2 study in ERBB2-mutated NSCLC reported objective response and clinical benefit in 19% (8/43) and 51% (22/43) of patients treated with neratinib plus the mTOR inhibitor temsirolimus, compared with 0% (0/17) and 35% (6/17) for patients treated with single-agent neratinib; exon 20 insertions were the most common ERBB2 mutation[255-256] .

Trastuzumab

Assay findings association

ERBB2
V659E

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved as monotherapy and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma. Trastuzumab biosimilars are also FDA approved for these indications. Please see the drug label(s) for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[39-40,44,59,257-261] .

SUPPORTING DATA

In a Phase 2a basket trial (MyPathway), trastuzumab plus pertuzumab treatment in non-small cell lung cancer (NSCLC) elicited PRs in 2/16 patients with ERBB2 amplification or overexpression and in 3/14 patients with HER2 mutation[259]. A Phase 2 trial of docetaxel with trastuzumab for the treatment of NSCLC reported PRs for 8% of patients, although the response did not correlate with HER2 status as assessed by immunohistochemistry[262]. Another Phase 2 study of 169 patients with NSCLC reported an ORR of 23% (7/30) with combination therapy of docetaxel and trastuzumab and 32% (11/34) with paclitaxel and trastuzumab; HER2 expression did not impact the results of this study[263]. A patient with lung adenocarcinoma that was HER-positive by FISH and harbored an ERBB2 G776L mutation experienced a PR on trastuzumab and paclitaxel[42]. In a retrospective analysis of patients with NSCLC harboring ERBB2 exon 20 insertion mutations, disease control was reported in 93% of patients (13/14) treated with trastuzumab in combination with chemotherapy[44].

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
V659E

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. These therapies are FDA approved in combination for the treatment of patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to trastuzumab in combination with pertuzumab[46,259,264-268] .

SUPPORTING DATA

In the Phase 2a MyPathway basket trial, trastuzumab plus pertuzumab treatment in patients with ERBB2-positive (amplification or overexpression) non-small cell lung cancer (NSCLC) achieved an ORR of 30% (7/27)[259,269] . The combination of trastuzumab, pertuzumab, and docetaxel was evaluated in patients with ERBB2-mutated (missense mutation or exon 20 insertion) NSCLC lacking mutations in known driver genes and reported a 29% (13/45) ORR, 6.8-month median PFS, and 17.6-month median OS[270].

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies

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

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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
ERBB2

ALTERATION
V659E

RATIONALE
ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors.

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Beijing City (China), Beijing (China), Chengdu City (China)

NCT04706949

PHASE 2

Pyrotinib Combined With Pemetrexed Plus Carboplatin in the First-line Treatment

TARGETS
EGFR, ERBB2

LOCATIONS: Shanghai (China)

NCT04579380

PHASE 2

Basket Study of Tucatinib and Trastuzumab in Solid Tumors With HER2 Alterations

TARGETS
ERBB2, ER

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Osakasayama (Japan), Nagoya-shi (Japan), Kawasaki-shi (Japan), Chuo-ku (Japan), Tokyo (Japan), Kashiwa-shi (Japan), Poznan (Poland), Liege (Belgium)

NCT05016544

PHASE 1/2

Inetetamab in Combination With Pyrotinib in HER2 Mutant or Amplified Advanced Non-small Cell Lung Cancer

TARGETS
ERBB2, EGFR

LOCATIONS: Guangzhou (China)

NCT04402008

PHASE 1/2

Study of Poziotinib in Japanese Patients With NSCLC

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Miyakojima-ku (Japan), Sunto District (Japan), Kashiwa (Japan)

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NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, PD-L1, ERBB2, PI3K-alpha, RET, AKTs

LOCATIONS: Alaska, Washington, Oregon, California, Idaho

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

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03810872

PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Liège (Belgium), Brussels (Belgium), Gent (Belgium)

NCT04983238

PHASE 1/2

Evaluation of Safety and Efficacy of Sodium Thiosulfate (BYON5667) Eye Drops to Reduce Ocular Toxicity in Cancer Patients Treated With SYD985

TARGETS
ERBB2

LOCATIONS: Antwerp (Belgium), Leuven (Belgium), Lille (France), Paris (France), Bordeaux (France), Barcelona (Spain), Llobregat (Spain), Lleida (Spain), Madrid (Spain)

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GENE
STK11

ALTERATION
L105*

RATIONALE
Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT03334617

PHASE 2

Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy.

TARGETS
PD-L1, PARP, mTORC1, mTORC2, ATR, CD73, STAT3

LOCATIONS: Seoul (Korea, Republic of), Berlin (Germany), Wien (Austria), Salzburg (Austria), Innsbruck (Austria), Esslingen a.N. (Germany), Heidelberg (Germany), Edmonton (Canada), Paris (France), Villejuif (France)

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

CUL3
E91D

HNF1A
I618M

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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 or WTX)	**APC**
AR	**ARAF** Exons 4, 5, 7, 11, 13, 15, 16	ARFRP1	ARID1A	ASXL1	**ATM**	**ATR**	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BCR* Introns 8, 13, 14	**BRAF** Exons 11-18, Introns 7-10	**BRCA1** Introns 2, 7, 8, 12, 16, 19, 20	**BRCA2** Intron 2	BRD4	BRIP1	BTG1
BTG2	**BTK** Exons 2, 15	CALR	CARD11	CASP8	CBFB	CBL	**CCND1**	CCND2
CCND3	CCNE1	CD22	CD70	CD74* Introns 6-8	CD79A	CD79B	**CD274** (PD-L1)	CDC73
CDH1	**CDK12**	**CDK4**	**CDK6**	CDK8	CDKN1A	CDKN1B	**CDKN2A**	CDKN2B
CDKN2C	CEBPA	CHEK1	**CHEK2**	CIC	CREBBP	**CRKL**	CSF1R	CSF3R
CTCF	CTNNA1	**CTNNB1** Exon 3	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1
DDR2 Exons 5, 17, 18	DIS3	DNMT3A	DOT1L	EED	**EGFR** Introns 7, 15, 24-27	EMSY (C11orf30)	EP300	EPHA3
EPHB1	EPHB4	**ERBB2**	**ERBB3** Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25	ERBB4	ERCC4	ERG	**ERRFI1**	**ESR1** Exons 4-8
ETV4* Intron 8	ETV5* Introns 6, 7	**ETV6*** Introns 5, 6	EWSR1* Introns 7-13	**EZH2** Exons 4, 16, 17, 18	EZR* Introns 9-11	FANCA	FANCC	FANCG
FANCL	FAS	FBXW7	FGF10	FGF12	FGF14	FGF19	FGF23	FGF3
FGF4	FGF6	**FGFR1** Introns 1, 5, Intron 17	**FGFR2** Intron 1, Intron 17	**FGFR3** Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17	FGFR4	FH	FLCN	FLT1
FLT3 Exons 14, 15, 20	**FOXL2**	FUBP1	GABRA6	GATA3	GATA4	GATA6	GID4 (C17orf39)	**GNA11** Exons 4, 5
GNA13	**GNAQ** Exons 4, 5	**GNAS** Exons 1, 8	GRM3	GSK3B	H3-3A (H3F3A)	HDAC1	HGF	HNF1A
HRAS Exons 2, 3	HSD3B1	ID3	**IDH1** Exon 4	**IDH2** Exon 4	IGF1R	IKBKE	IKZF1	INPP4B
IRF2	IRF4	IRS2	JAK1	**JAK2** Exon 14	**JAK3** Exons 5, 11, 12, 13, 15, 16	JUN	KDM5A	KDM5C
KDM6A	KDR	KEAP1	KEL	**KIT** Exons 8, 9, 11, 12, 13, 17, Intron 16	KLHL6	KMT2A (MLL) Introns 6, 8-11, Intron 7	KMT2D (MLL2)	

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APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

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

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF THERAPIES AND CLINICAL TRIALS

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

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

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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.

REPORT HIGHLIGHTS

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

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SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version 6.2.0

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