FOUNDATIONONE® LIQUID CDx

PATIENT

TUMOR TYPE
Lung cancer (NOS)
COUNTRY CODE
PE

REPORT DATE
28 Dec 2021
ORDERED TEST #
ORD-1265581-01

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 cancer (NOS)
DATE OF BIRTH 09 June 1962
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN
MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN ID OSV 06/09/1962
SPECIMEN TYPE Blood
DATE OF COLLECTION 09 December 2021
SPECIMEN RECEIVED 19 December 2021

Biomarker Findings

Blood Tumor Mutational Burden - 1 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 A775_G776insYVMA
IDH1 R132H
APC S1545*
DNMT3A W860R
TP53 S127F

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Ado-trastuzumab emtansine** (p. 11), **Fam-trastuzumab deruxtecan** (p. 11)
- Targeted therapies with **potential resistance** based on this patient's genomic findings: **Lapatinib** (p. 14)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 15)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A*** **W860R** (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 1 Muts/Mb	**No therapies or clinical trials. See Biomarker Findings section**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
Tumor Fraction - Elevated Tumor Fraction Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).**

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GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ERBB2 -	A775_G776insYVMA	0.63%	Afatinib	Ado-trastuzumab emtansine 2A Fam-trastuzumab deruxtecan 2A Trastuzumab Trastuzumab + Pertuzumab *Lapatinib* ⊗
10 Trials see p. 15				
IDH1 -	R132H	0.60%	None	Ivosidenib
10 Trials see p. 17				

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *NCCN category*

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

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

DNMT3A - W860R ..... p. 8

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.

APC - S1545* ..... p. 7
DNMT3A - W860R ..... p. 8
TP53 - S127F ..... p. 9

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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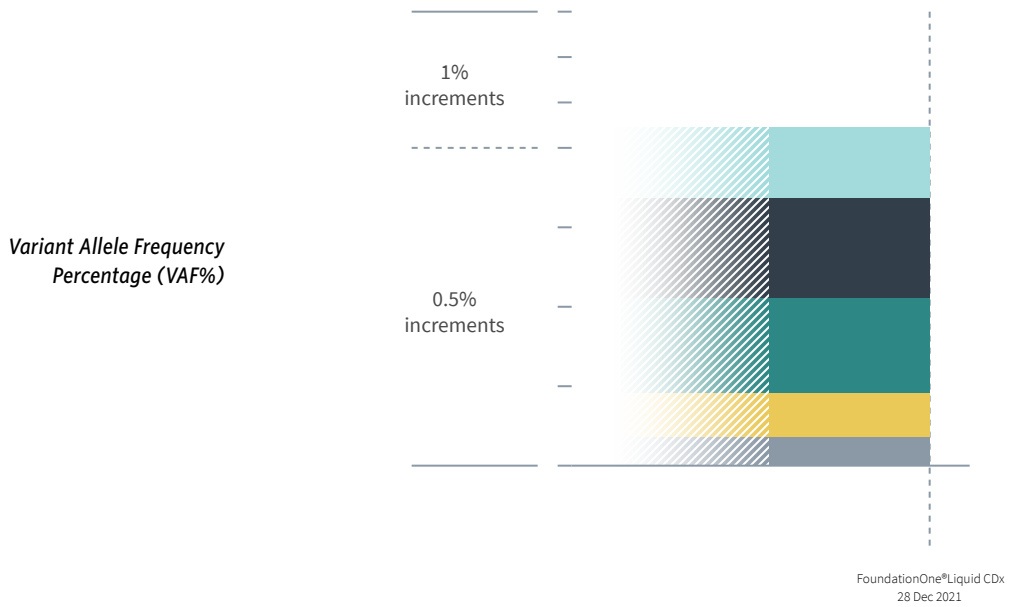

HISTORIC PATIENT FINDINGS		ORD-1265581-01 VAF%
Blood Tumor Mutational Burden		1 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
ERBB2	A775_G776insYVMA	0.63%
IDH1	R132H	0.60%
APC	S1545*	0.28%
DNMT3A	W860R	0.77%
TP53	S127F	0.18%

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

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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
1 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 large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[7]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[8]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[8-9].

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[10-11] and cigarette smoke in lung cancer[12-13], treatment with temozolomide-based chemotherapy in glioma[14-15], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[16-20], and microsatellite instability (MSI)[16,19-20]. 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[21-26].

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)[27]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[28], Ewing sarcoma and osteosarcoma[29], prostate cancer[24], breast cancer[30], leiomyosarcoma[31], esophageal cancer[32], colorectal cancer[33], and gastrointestinal cancer[34].

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[35], 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[36-37].

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GENE
ERBB2

ALTERATION
A775_G776insYVMA

TRANSCRIPT ID
NM_004448

CODING SEQUENCE EFFECT
2324_2325insATACGTGATGGC

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[38-43], pertuzumab in combination with trastuzumab[40,44-46], and zanidatamab (ZW25)[47], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[48] and fam-trastuzumab deruxtecan[49], HER2 kinase inhibitors such as tucatinib[50-53], and dual EGFR/HER2 kinase inhibitors such as lapatinib[54-62], afatinib[43,63-72], neratinib[73-76], dacomitinib[77], and pyrotinib[78-79] . Early clinical studies aimed at preventing or overcoming resistance to anti-HER2 therapies are underway, including agents targeting the PI3K-AKT pathway or HSP90[80-81]. A Phase 1 basket trial of pyrotinib demonstrated an ORR of 17.4% (4/23) for ERBB2-altered solid tumors, with PRs for 1 patient each with HER2-positive salivary, biliary, ovarian, or endometrial cancers[82]. Clinical data in solid tumors other than NSCLC and extra-mammary Pagets disease of the skin are limited; a Phase 2 study of afatinib for patients with solid tumors and ERBB2 activating mutations reported an ORR of 2.7% and a 6-month progression-free survival rate of 11%, missing its primary endpoint[83]. Second-generation TKIs dacomitinib and neratinib have elicited modest response rates in patients with ERBB2 exon 20 insertions, with reported ORRs of 3.8% to 12%, DCRs of 20% to 42% across two studies, and median PFS of 3.0 to 5.5 months for patients with non-small cell lung cancer (NSCLC)[75,77]. Phase 2 studies of poziotinib, a selective inhibitor targeting EGFR and ERBB2 exon 20 mutations reported ORRs of 27% to 35%, DCRs of 70% to 73%, and median PFS (mPFS) of 5.5 months in patients with NSCLC harboring ERBB2 exon 20 insertions who had received prior treatment[84]. For treatment naive patients with NSCLC harboring ERBB2 exon 20 insertions who received poziotinib, a Phase 2 trial reported 44% (21/48) ORR, 75% (36/48) DCR, and mPFS of 5.6 months[85]. The irreversible EGFR/ERBB2 inhibitor pyrotinib achieved ORRs of 32% to 53%, DCRs of 40% to 73%, and median PFS of 6.4 to 6.8 months in Phase 2 studies in previously treated, ERBB2-mutated NSCLC, with responses observed across a variety of exon 20 insertions and point mutations[86]. A Phase 2 study of EGFR/ERBB2 inhibitor tarloxotinib reported a 22% (2/9) ORR and a 67% (6/9) DCR in NSCLC with ERBB2 exon 20 insertions[87]. Antibodies targeting ERBB2 have also been tested against exon 20 insertions. Phase 2 studies have reported activity for T-DM1 in previously treated, ERBB2-mutated NSCLC, including for patients with ERBB2 exon 20 insertions[88-89]. Several case studies also report benefit from trastuzumab for patients with lung or breast cancer harboring ERBB2 exon 20 insertions[43,90-92]. Second-generation TKI afatinib has elicited modest response rates in patients with ERBB2 exon 20 insertions, with reported ORRs of 7.7% to 33.3% and DCRs of 53.8% to 69.6% across several studies, and median PFS of 3.2 to 4.5 months for patients with NSCLC[68-72].

— Potential Resistance —

Clinical and preclinical data suggest that ERBB2 exon 20 insertions confer resistance to lapatinib and reduced sensitivity to afatinib, dacomitinib, and neratinib[43,69-70,75,77,93-98]. However, it is unclear if ERBB2 exon 20 insertions confer reduced sensitivity to lapatinib in combination with other therapies, such as trastuzumab.

FREQUENCY & PROGNOSIS

ERBB2 mutations have been reported in 2.2–4.2% of lung adenocarcinomas and lung squamous cell carcinomas across several genomic studies[99-104]. Exon 20 insertions are the most frequently observed ERBB2 alteration in lung adenocarcinomas, representing 61% (72/118) to 96% (24/25) of ERBB2 mutations detected[71,105]. One large study of 20,656 patients with non-small cell lung cancer reported 24% of ERBB2 mutations were exon 20 insertions[106]. Of ERBB2 exon 20 insertions in NSCLC, A775_G776insYVMA is the most common (42–85%), followed by P780_Y781insGSP (9–11%) and G776>VC (8–11%)[70-71,96,105]. Exon 20 insertion mutations are more prevalent in adenocarcinoma histology[70] and are generally mutually exclusive with other common driver alterations in NSCLC[105]. HER2 overexpression has been documented in 11-32% of NSCLC cases, and is generally reported more frequently in non-squamous histologies[107-108]. Expression of HER2 has generally been associated with poor prognosis in NSCLC in several studies[109-113]. In a retrospective study of patients with ERBB2-mutated NSCLC who were treated with afatinib, A775_G776insYVMA predicted inferior PFS when compared with other exon 20 insertions (HR = 0.009) or missense mutations (HR = 0.184), whereas P780_Y781insGSP and G776>VC were associated with improved PFS compared with missense mutations (HR = 0.050)[71].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. ERBB2 exon 20 insertion mutations, such as observed here, are predicted to be activating[95-96,114-116]. The mutation seen here is similar to A775_G776insYVMA (also known as A771_Y772insYVMA or Y772_A775dup), which is the most common exon 20 insertion mutation across cancer types[96].

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GENE
IDH1

ALTERATION
R132H

TRANSCRIPT ID
NM_005896

CODING SEQUENCE EFFECT
395G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

IDH1 mutations that lead to production of 2-HG, most commonly R132 alterations, may predict sensitivity to IDH1-mutation-specific inhibitors such as ivosidenib[117]. A Phase 1b/2 study of the IDH1 inhibitor olutasidenib for patients with IDH1-mutated glioma reported a DCR of 50% (n=24) with 1 PR[118]. A Phase 1 study of the pan-IDH1/IDH2 inhibitor vorasidenib for patients with IDH1- or IDH2-mutated glioma reported an ORR of 18.2% (4/22; RANO criteria) and median PFS of 31.4 months for non-enhancing cases and median PFS of 7.5 months for the overall glioma population (n=52)[119]. Preclinical studies suggested that IDH1 neomorphic mutations may also confer sensitivity to PARP inhibitors[120-123].

FREQUENCY & PROGNOSIS

IDH1 mutations are uncommon in lung adenocarcinoma and lung squamous cell carcinoma, reported in 1% of cases in the TCGA datasets[101,104]. Additional studies of lung cancer tissues and cell lines have failed to find IDH1 mutations[124-125]. Plasma levels of IDH1 protein are increased in patients with non-small cell lung cancer (NSCLC) and may have diagnostic value, particularly in patients with lung adenocarcinoma[126]. Increased expression of IDH1 has been correlated with shorter overall survival in patients with NSCLC[127].

FINDING SUMMARY

The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis[128]. R132 is located within the active site of IDH1 and is a hotspot for mutations in cancer[128-132]. Substitutions at IDH1 R132 alter the enzymatic activity of IDH1, resulting in the production of the oncometabolite, D-2-hydroxyglutarate (2-HG)[130-134], which promotes tumorigenesis[130,135-138].

GENE
APC

ALTERATION
S1545*

TRANSCRIPT ID
NM_000038

CODING SEQUENCE EFFECT
4634C>G

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors. Preclinical studies have reported that APC inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated[139]. In addition, the COX-2 inhibitor celecoxib was shown to reduce WNT signaling in cancer cell lines[140-141]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[142].

FREQUENCY & PROGNOSIS

In the TCGA datasets, APC mutations have been reported in 3.9% of lung adenocarcinomas[101] and 4.5% of lung squamous cell carcinoma samples analyzed[104]. Studies of APC in lung cancer have reported mutations in 5-7% of non-small cell lung cancer (NSCLC) tumors examined[143-144]. In contrast, loss of heterozygosity at the APC/MCC locus has been reported in up to 68% (17/25) of NSCLC, with a higher incidence in squamous cell carcinomas compared to adenocarcinomas[145-146]. Hypermethylation of APC in NSCLC tumors has been reported in a number of studies[147-150]; hypermethylation and lower APC mRNA expression have been associated with poorer survival in patients with NSCLC[146,151]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[152].

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[153]. Alterations such as seen here may disrupt APC function or expression[154-158].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[159-161]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[162], and in the appropriate clinical context germline testing of APC is recommended.

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GENE
DNMT3A

ALTERATION
W860R

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
2578T>C

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2021)[163-164]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2021).

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[165-166]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[149,167-171]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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[172-177]. 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[172-173]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[178]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[176,179-180]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
TP53

ALTERATION
S127F

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
380C>T

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[181-184], or p53 gene therapy and immunotherapeutics such as SGT-53[185-189] and ALT-801[190]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[191]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[192]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[193]. 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[194]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[195]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[196]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[189]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[197]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[198-200]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[201]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[202-203]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[204-205]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[101,104,206-211], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[101-102,104,212]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[163-164]. 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[213]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[214].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[215]. Alterations such as seen here may disrupt TP53 function or expression[216-220].

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 2021)[221]. 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[222-224], including sarcomas[225-226]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[227] to 1:20,000[226]. 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[228]. 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[172-177]. 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[172-173]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[178]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[176,179-180]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Afatinib

Assay findings association

ERBB2
A775_G776insYVMA

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[68-72,95-98] . Studies have reported DCRs of 54-70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[68-72] . Retrospective data suggest that ERBB2 A775_G776insYVMA may predict inferior PFS with afatinib in patients with NSCLC, as compared with other exon 20 insertions (HR = 0.009) or ERBB2 missense mutations (HR = 0.184)[71].

SUPPORTING DATA

The Phase 2 NICHE trial for platinum-refractory non-small cell lung cancer (NSCLC) harboring ERBB2 exon 20 insertions reported a low ORR but a high DCR, with 1 PR and 7 SDs out of 13 patients; the median PFS (mPFS) and OS were 3.7 and 13 months, respectively[68]. A retrospective study of afatinib for patients with ERBB2-mutated NSCLC, most of whom were previously treated, reported an ORR of 16% and a DCR of 69%; the mPFS was 1.2 months for patients with A775_G776insYVMA, 7.6 months for patients with G776>VC or P780_Y781insGSP, and 3.6 months for patients with ERBB2 missense mutations[71]. Other retrospective studies of afatinib for ERBB2-mutated lung cancer have reported similar ORRs of 13–16% and DCRs of 68–70%[69-70] . A case report of a patient with lung adenocarcinoma harboring an ERBB2 V659E activating mutation demonstrated a PR of 9 months in response to afatinib as well as near resolution of a metastatic lesion in the liver[229]. 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[230-236] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[43,65-69,71-72,93,95,237-238] . 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[235]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[239].

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Ado-trastuzumab emtansine

Assay findings association

ERBB2
A775_G776insYVMA

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[48,89,240-254] . Patients with NSCLC and various ERBB2 exon 20 insertion mutations have benefited from T-DM1[88-89,255] .

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)[242]. 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)[89]. 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[93,255] .

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
A775_G776insYVMA

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)[256-257] , ERBB2 mutation may predict sensitivity to fam-trastuzumab deruxtecan. On the basis of clinical data in non-small cell lung cancer (NSCLC)[256-257] , ERBB2 exon 20 insertions 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[257] and ERBB2-overexpressing cohorts[258]. 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[257]. In the ERBB2-overexpressing cohort, the ORR and DCR were 25% (12/49) and 69% (34/49), respectively[258]. 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[256]. 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[256]. 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[242].

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Ivosidenib

Assay findings association

IDH1
R132H

AREAS OF THERAPEUTIC USE

Ivosidenib is an isocitrate dehydrogenase 1 (IDH1) inhibitor that is FDA approved to treat patients with a susceptible IDH1 mutation in relapsed or refractory acute myeloid leukemia (AML) or previously treated locally advanced or metastatic cholangiocarcinoma. It is also approved as a first-line treatment for patients with AML and a susceptible IDH1 mutation who are not eligible for intensive induction chemotherapy or who are ≥75 years old. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in AML[259] and cholangiocarcinoma[260-261] and limited clinical data in myelodysplastic syndrome (MDS)[259] and glioma[117,262] , IDH1 R132 mutation may confer sensitivity to ivosidenib.

SUPPORTING DATA

Clinical data on the efficacy of ivosidenib for the treatment of NSCLC are limited (PubMed, Sep 2021). Ivosidenib has shown clinical activity in diverse IDH1-mutated solid tumor types. In the Phase 3 ClaIDHy trial, patients with IDH1 R132-mutated cholangiocarcinoma treated with ivosidenib, compared to placebo, had a significantly increased PFS (HR=0.37, p<0.001) and numerically increased OS (HR=0.79, p=0.093) that became significant once adjusted for crossover (HR=0.49, p<0.0001)[261,263] . For patients with glioma, treatment with ivosidenib resulted in high rates of SD (72.7% [8/11] and 87.5% [21/24] for patients in the dose escalation and expansion cohorts, respectively)[264]. A cohort of patients with chondrosarcoma that harbored a high incidence of IDH1 R132 mutation (n=15/21) achieved a high rate of SD (55.0% [11/20]), including 3 SDs >1.5 years[265]. In a Phase 1 trial for patients with IDH1-mutated solid tumors, including chondrosarcoma, cholangiocarcinoma, and glioma, ivosidenib led to 4 PRs[117].

Trastuzumab

Assay findings association

ERBB2
A775_G776insYVMA

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

Trastuzumab-involving regimens elicited significant responses in patients with certain ERBB2 mutations[42-43,58,90,93,266] . Patients with NSCLC and ERBB2 exon 20 insertions, including A775_G776insYVMA and G776>VC, have benefited from treatment with trastuzumab[42-43,90-91,93] , with reported DCRs of 75–96% for trastuzumab in combination with chemotherapy[43,93] .

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[267]. 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[268]. 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[269]. A patient with lung adenocarcinoma that was HER-positive by FISH and harbored an ERBB2 G776L mutation experienced a PR on trastuzumab and paclitaxel[41]. 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[43].

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Trastuzumab + Pertuzumab

Assay findings association

ERBB2
A775_G776insYVMA

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[45,267,270-274] .

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 26% (7/27)[267,275] . The combination of trastuzumab, pertuzumab, and docetaxel was evaluated in patients with ERBB2-mutated 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[276].

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Lapatinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

ERBB2
A775_G776insYVMA

AREAS OF THERAPEUTIC USE

Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine to treat patients with HER2-overexpressing (HER2+) metastatic breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib[54-62] . On the basis of clinical and preclinical evidence, ERBB2 exon 20 insertions confer resistance to lapatinib[43,93-97] . However, it is unclear if ERBB2 exon 20 insertions confer reduced sensitivity to lapatinib in combination with other therapies, such as trastuzumab.

SUPPORTING DATA

Prospective[94] and retrospective studies[43,93] reported PD for multiple patients with NSCLC and ERBB2 exon 20 insertions treated with lapatinib in either the first or later line setting. Clinical data on the efficacy of lapatinib have primarily been in the context of breast cancer. A Phase 1 study lapatinib monotherapy included 9 unselected patients with lung cancer and reported 1 case of prolonged SD[277]. Additionally, patients with ERBB2-mutated lung cancer have experienced limited partial responses to lapatinib plus chemotherapy in case reports[54,57,278] . In a Phase 2 trial in patients with advanced or metastatic NSCLC, lapatinib monotherapy did not result in significant tumor reduction, but further investigation of lapatinib in combination with other therapies may be warranted[279].

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
A775_G776insYVMA

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. Clinical and preclinical data suggest that ERBB2 exon 20 insertions confer resistance to lapatinib and reduced sensitivity to afatinib, dacomitinib, and neratinib. However, it is unclear if ERBB2 exon 20 insertions confer reduced sensitivity to lapatinib in combination with other therapies, such as trastuzumab. Retrospective clinical data suggest that ERBB2 A775_G776insYVMA is associated with inferior PFS with afatinib, compared with other ERBB2 mutations or exon 20 insertions. Investigational agents such as poziotinib and pyrotinib, or ERBB2-targeted antibodies such as trastuzumab and T-DM1, may be more effective.

NCT04447118

PHASE 3

Phase 3 Study of Pyrotinib Versus Docetaxel in Patients With Advanced Non-squamous NSCLC Harboring a HER2 Exon 20 Mutation Who Failed Platinum Based Chemotherapy

TARGETS
EGFR, ERBB2

LOCATIONS: Florida, Texas, Tennessee, New York, Kansas, California, Washington

NCT04589845

PHASE 2

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

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

LOCATIONS: Sao Paulo (Brazil), Florida, Alabama, Texas, Georgia, South Carolina

NCT02693535

PHASE 2

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

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

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Pennsylvania, Indiana

NCT02795156

PHASE 2

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

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

LOCATIONS: Florida, Tennessee, Missouri, Wisconsin, Colorado

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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
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Florida, Louisiana, Tennessee, Texas, New Jersey, Missouri

NCT02393248

PHASE 1/2

Open-Label, Dose-Escalation Study of INCB054828 in Subjects With Advanced Malignancies

TARGETS
PD-1, FGFR1, FGFR2, FGFR3, ERBB2

LOCATIONS: Florida, Texas, New Jersey

NCT03318939

PHASE 2

Phase 2 Study of Poziotinib in Patients With NSCLC With EGFR or HER2 Exon 20 Insertion Mutation

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Florida, Texas, Georgia, North Carolina, Virginia, District of Columbia, Maryland

NCT02716116

PHASE 1/2

A Trial of AP32788 in Non-Small Cell Lung Cancer

TARGETS
EGFR, ERBB2

LOCATIONS: Florida, Georgia, North Carolina, Virginia, Arizona, California

NCT03066206

PHASE 2

Poziotinib in EGFR Exon 20 Mutant Advanced Non-Small Cell Lung Cancer (NSCLC)

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Texas

NCT03805841

PHASE 2

Phase 2 Study of Tarloxotinib in Patients With NSCLC Harboring EGFR Exon 20 Insertion or HER2-activating Mutations

TARGETS
ERBB2, EGFR

LOCATIONS: Georgia, District of Columbia, Pennsylvania, Michigan, Illinois, Toronto (Canada), Colorado, California

GENE
IDH1

ALTERATION
R132H

RATIONALE
IDH1 mutations may predict sensitivity to IDH1 inhibitors. On the basis of preclinical data, IDH1 mutations may also confer sensitivity to PARP inhibitors in solid tumors.

NCT04380636

PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Lima (Peru), Arequipa (Peru), Antofagasta (Chile), Vina del Mar (Chile), Santiago (Chile), Temuco (Chile), Orizaba (Mexico), Florida

NCT04475939

PHASE 3

Placebo-controlled Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants With Advanced/Metastatic Non-small Cell Lung Cancer

TARGETS
PD-1, PARP

LOCATIONS: Rosario (Argentina), Cipoletti (Argentina), Florida (Argentina), Ciudad Autonoma de Buenos Aires (Argentina), Curitiba (Brazil), Porto Alegre (Brazil), Belo Horizonte (Brazil), Cachoeiro Do Itapemirim (Brazil), Texas, Georgia

NCT04624204

PHASE 3

Placebo-controlled, Study of Concurrent Chemoradiation Therapy With Pembrolizumab Followed by Pembrolizumab and Olaparib in Newly Diagnosed Treatment-Naïve Limited-Stage Small Cell Lung Cancer (LS-SCLC) (MK 7339-013/KEYLYNK-013)

TARGETS
PARP, PD-1, TOP2

LOCATIONS: Guadalajara (Mexico), Monterrey (Mexico), South Carolina, Louisiana, Tennessee, District of Columbia, Maryland, Pennsylvania, New York, New Jersey

NCT04334941

PHASE 2

Testing Maintenance Therapy for Small Cell Lung Cancer in Patients With SLFN11 Positive Biomarker

TARGETS
PD-L1, PARP

LOCATIONS: Florida, Louisiana

NCT03221400

PHASE 1/2

PEN-866 in Patients With Advanced Solid Malignancies

TARGETS
PARP, HSP90

LOCATIONS: Florida, South Carolina, Tennessee, Arkansas, Virginia, Maryland, Oklahoma

NCT02498613

PHASE 2

A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors

TARGETS
PARP, VEGFRs

LOCATIONS: Florida, Texas, Tennessee, Virginia, Connecticut, Massachusetts, Toronto (Canada), California

Electronically signed by Matthew Hiemenz, M.D. | 28 December 2021
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NCT03672773

PHASE 2

Talazoparib and Low-Dose Temozolomide in Treating Participants With Relapsed or Refractory Extensive-Stage Small Cell Lung Cancer

TARGETS
PARP

LOCATIONS: Florida, Kansas, Indiana, California

NCT03212274

PHASE 2

Olaparib in Treating Patients With Advanced Glioma, Cholangiocarcinoma, or Solid Tumors With IDH1 or IDH2 Mutations

TARGETS
PARP

LOCATIONS: Florida, Texas, North Carolina, Tennessee, Oklahoma, Maryland, Missouri, Ohio

NCT03878095

PHASE 2

Testing Olaparib and AZD6738 in IDH1 and IDH2 Mutant Tumors

TARGETS
ATR, PARP

LOCATIONS: Florida, Texas, Maryland, Ohio, Connecticut, Michigan, Wisconsin, Utah

NCT03532880

PHASE 1

A Study of Olaparib and Low Dose Radiotherapy for Small Cell Lung Cancer

TARGETS
PARP

LOCATIONS: Florida, New Jersey, New York

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.

BAP1	***CREBBP***	***GNA11***	***PTCH1***
S90C	M810L	F341V	V1263I

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ORDERED TEST # ORD-1265581-01

APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*
CD274 **(PD-L1)**	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*
CDKN2A	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***
CSF1R	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*
DAXX	*DDR1*	***DDR2*** **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***
ESR1 **Exons 4-8**	*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FAM46C*	*FANCA*
FANCC	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*
FLCN	*FLT1*	***FLT3*** **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3F3A*	*HDAC1*	*HGF*
HNF1A	***HRAS*** **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*
INPP4B	*IRF2*	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)

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

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also 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. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

MR Suite Version 5.2.0

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