Rapport remis à titre d'exemple, valide en date du 23/10/2023

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)
- NAME
- DATE OF BIRTH
- SEX
- MEDICAL RECORD #

PHYSICIAN
- ORDERING PHYSICIAN
- MEDICAL FACILITY
- ADDITIONAL RECIPIENT
- MEDICAL FACILITY ID
- PATHOLOGIST

SPECIMEN
- SPECIMEN ID
- SPECIMEN TYPE
- DATE OF COLLECTION
- SPECIMEN RECEIVED

Genomic Signatures

Blood Tumor Mutational Burden - 6 Muts/Mb
Microsatellite status - MSI-High Not Detected
ctDNA Tumor Fraction - High (13%)

Gene Alterations

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

ERBB2 G776>VC
TP53 C176F

This assay tested >300 cancer-related genes, including the following **8** gene(s) routinely assessed in this tumor type: ***ALK***, ***BRAF***, ***EGFR***, ***ERBB2***, ***KRAS***, ***MET***, ***RET***, ***ROS1***.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Trastuzumab deruxtecan** (p. 11), **Trastuzumab emtansine** (p. 12)
- **High ctDNA Tumor Fraction** was detected, indicating a lower risk of false negative results (p. 5).
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials. See Genomic Signatures section**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
ctDNA Tumor Fraction - High (13%)	**High ctDNA Tumor Fraction defined as ≥1.0% based on concordance for defined short variants and fusions. See Genomic Signatures Finding Summary.**

GENE ALTERATIONS		VAF%
ERBB2 -	G776>VC	18.4%

10 Trials see p. 13

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

(?) *Limited evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *NCCN category*

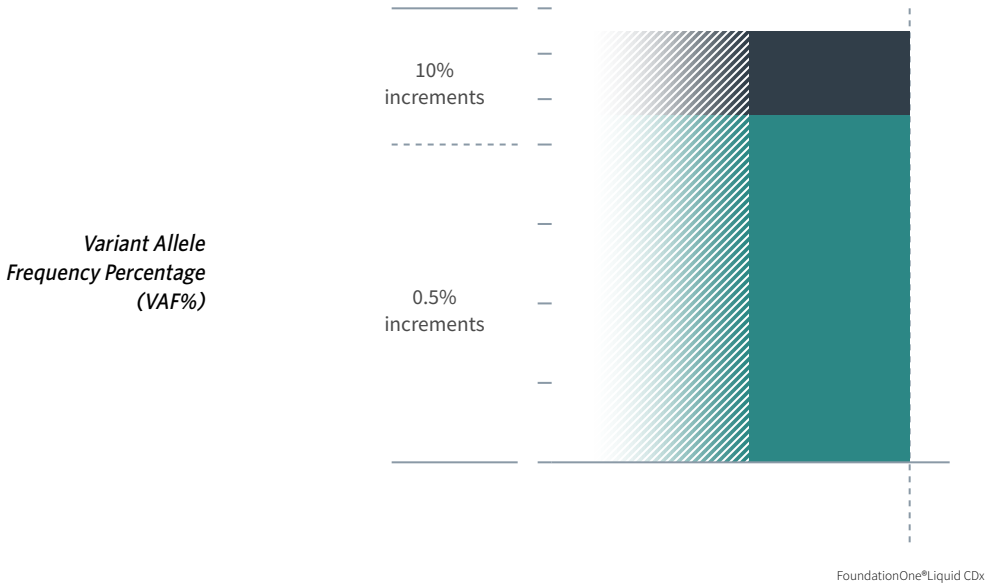
GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

TP53 - C176F ..... p. 7

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 through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally in some EU Member States but may not be available in your Member State: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, and Triptorelin. The Summary of Product Characteristics of EU-approved therapies are available at https://www.ema.europa.eu/en/medicines. The information available on EMA's website is updated in regular intervals but may not reflect the current status at any time. 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.



HISTORIC PATIENT FINDINGS (Genomic Signatures)		ORD-XXXXXXX-XX
Blood Tumor Mutational Burden		6 Muts/Mb
Microsatellite status		MSI-High Not Detected
ctDNA Tumor Fraction		13%
HISTORIC PATIENT FINDINGS (Gene Alterations)		**VAF%**
ERBB2	● G776>VC	18.4%
TP53	● C176F	8.6%

IMPORTANT NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx 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. Variants reported for prior time points reflect reporting practices at the time of the historical test(s). Changes in variant reporting nomenclature, classification, or handling may result in the appearance of discrepancies across time points. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

ctDNA Tumor Fraction may include previous Tumor Fraction results which reflect reporting practices at the time of reporting. Changes in biomarker reporting may result in the appearance of discrepancies across time points.

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

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

Please note that other aspects of this table may have changed from the previous version to reflect the most up-to-date reporting information.

GENOMIC SIGNATURE

Blood Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased blood tumor mutational burden (bTMB) may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1[3-4], anti-PD-1/CTLA4 therapies[5-6] , anti-PD-L1/CTLA4 therapies[7-10]. A Phase 2 multi-solid-tumor trial showed that bTMB ≥16 Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor[5]. In non-small cell lung cancer (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 Muts/Mb-16 Muts/Mb[1,8-10]. In head and neck squamous cell carcinoma (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[11]. In colorectal cancer (CRC), a Phase 2 study showed that bTMB TMB ≥28 Muts/Mb (approximate equivalency ≥14 Muts/Mb as measured by this assay) was associated with improved OS from a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[7].

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)[4]. 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[12]. 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[13]. 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[14]. 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)[15]. 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[16]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[16-17].

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[18-19] and cigarette smoke in lung cancer[20-21], treatment with temozolomide-based chemotherapy in glioma[22-23], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[24-28], and microsatellite instability (MSI)[24,27-28]. 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[1-2,4]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

GENOMIC SIGNATURE

ctDNA Tumor Fraction

RESULT
High (13%)

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction 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. 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[29-34].

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)[35]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[36], Ewing sarcoma and osteosarcoma[37], prostate cancer[32], breast cancer[38], leiomyosarcoma[39], esophageal cancer[40], colorectal cancer[41], and gastrointestinal cancer[42].

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[43], 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[44-45].

GENE
ERBB2

ALTERATION
G776>VC

TRANSCRIPT ID
NM_004448.2

CODING SEQUENCE EFFECT
2326_2327insTCT

VARIANT CHROMOSOMAL POSITION
chr17:37880997

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[46-51], pertuzumab in combination with trastuzumab[48,52-54], and zanidatamab (ZW25)[55], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[56] and fam-trastuzumab deruxtecan (T-DXd)[57-59], HER2 kinase inhibitors such as tucatinib[60-63], and dual EGFR/HER2 kinase inhibitors such as lapatinib[64-72], afatinib[51,73-82], neratinib[83-86], dacomitinib[87], and pyrotinib[88-89] . The Phase I trial of HER2-selective TKI BI-1810631 for patients with HER2-aberration-positive metastatic solid tumors reported a 3.7% ORR (7/19) and an 84% DCR; for patients with NSCLC, a 45% ORR (5/11) and a 91% DCR were reported[90]. HER2 antibody drug conjugates trastuzumab emtansine[91] and trastuzumab deruxtecan have elicited ORRs of 44-55% among patients with ERBB2-mutated non-small cell lung cancer (NSCLC), including for patients with ERBB2 exon 20 insertions[59]. Tyrosine kinase inhibitors have demonstrated efficacy for patients with HER2 exon 20 insertions including poziotinib (ORR 27-28%)[92-93] and pyrotinib (ORR 30-53%)[94-95]. Other kinase inhibitors have been evaluated for patients with NSCLC harboring exon 20 insertions including afatinib (ORR 8-17%)[78-81], dacomitinib (ORR 12%)[87], and neratinib (ORR 4%)[85].

— Potential Resistance —

Clinical and preclinical data suggest that ERBB2 exon 20 insertions confer resistance to lapatinib and reduced sensitivity to afatinib, dacomitinib, and neratinib[51,79-80,85,87,96-101]. 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[102-107]. 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[81,108]. One large study of 20,656 patients with non-small cell lung cancer reported 24% of ERBB2 mutations were exon 20 insertions[109]. 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%)[80-81,99,108]. Exon 20 insertion mutations are more prevalent in adenocarcinoma histology[80] and are generally mutually exclusive with other common driver alterations in NSCLC[108]. HER2 overexpression has been documented in 11-32% of NSCLC cases, and is generally reported more frequently in non-squamous histologies[110-111]. Expression of HER2 has generally been associated with poor prognosis in NSCLC in several studies[112-116]. 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)[81].

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[98-99,117-119]. The mutation seen here is similar to G776>VC (also known as G776_V777>VCV, G776delinsVC, or G776_V777delinsVCV)[99].

GENE
TP53

ALTERATION
C176F

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
527G>T

VARIANT CHROMOSOMAL POSITION
chr17:7578403

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[120-123] or p53 gene therapy such as SGT53[124-128]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[129]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[130]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[131]. 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[132]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[133]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[134]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[135]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[128]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[136]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[137].

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)[104,107,138-143], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, 2023)[104-105,107,144-147]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, 2023)[146-147]. 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[148]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[149].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[150]. Alterations such as seen here may disrupt TP53 function or expression[151-155].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[156-158], including sarcomas[159-160]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[161] to 1:20,000[160]. 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[162]. 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[163-168]. 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[163-164]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[169]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[167,170-171]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Afatinib

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is available in the EU to treat patients with advanced non-small cell lung cancer (NSCLC) and activating EGFR mutations and for the treatment of patients with advanced 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[78-82,98-101] . Studies have reported DCRs of 54-70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[78-82] . Retrospective data suggest that ERBB2 G776>VC or P780_Y781insGSP may predict improved PFS with afatinib in patients with NSCLC as compared with ERBB2 missense mutations (HR = 0.050)[81].

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[78]. 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[81]. Other retrospective studies of afatinib for ERBB2-mutated lung cancer have reported similar ORRs of 13–16% and DCRs of 68–70%[79-80] . 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[172]. In the LUX-Lung 1 Phase 2b/3 trial for patients with advanced non-small cell lung cancer (NSCLC) who previously progressed on first-generation EGFR tyrosine kinase inhibitors, afatinib treatment resulted in longer median PFS (mPFS; 3.3 vs. 1.1 months, HR=0.38) but no significant difference in median OS (mOS; 10.8 vs. 12.0 months, HR=1.08) when compared with placebo[173]; similar results were observed in the single-arm LUX-Lung 4 trial in the same treatment setting[174]. The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer mOS (7.9 vs. 6.8 months, HR=0.81), significantly longer mPFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[175]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[176].

Dacomitinib

Resistance of variant(s) to associated therapy is unclear

Assay findings association

ERBB2
G776>VC

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 available in the EU for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) with EGFR activating mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Early phase clinical trials report anti-tumor activity of dacomitinib in advanced solid tumors with ERBB2 activating mutations[87,177] , ERBB2 amplification[178-179] or HER2 overexpression[180]. Sensitivity of ERBB2 exon 20 mutations to dacomitinib may depend on the specific variant, with mutations that include G770 being associated with sensitivity[181]. In a prospective Phase 2 study of dacomitinib in NSCLC, the ORR was 12% in patients with ERBB2 mutations, which were mostly exon 20 insertions; objective response was observed in 2 patients with G778_P780insGSP and 1 patient with M774delinsWLV, but not in patients with other exon 20 insertions[87]. Preclinical data support reduced sensitivity of ERBB2 exon 20 insertions to dacomitinib[99-101] .

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[87]. In ERBB2-amplified NSCLC, response rates of 0/4 (0%)[87] to 1/3 (33%)[179] have been reported, with disease control (PR or SD) achieved in 4/9 (44%) patients total[87,177,179] . 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[182]. Phase 1/2 studies of dacomitinib for patients with advanced KRAS-wildtype non-small cell lung cancer (NSCLC) who had previously progressed on chemotherapy and erlotinib or gefitinib and were not selected for EGFR mutations reported ORRs of 4.6-17% (3/66-9/53), median PFS of 3-4 months, and median OS of 9-11 months[179,183] .

Neratinib

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is available in the EU for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer who are less than 1 year from the completion of prior adjuvant trastuzumab treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[83-86,184-186] and preclinical[119,187-190] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib. A Phase 2 trial of neratinib in patients with solid tumors reported 1 CR, 1 PR, and 14 SD out of 25 evaluable patients with ERBB2 exon 20 insertion mutations, with both objective responses in patients with breast cancer[85].

Preclinical data support reduced sensitivity of ERBB2 exon 20 insertions to neratinib[99-100] .

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[85]. 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[191-192] .

Trastuzumab

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Trastuzumab-involving regimens elicited significant responses in patients with certain ERBB2 mutations[50-51,68,96,193-194] . Patients with NSCLC and ERBB2 exon 20 insertions, including A775_G776insYVMA and G776>VC, have benefited from treatment with trastuzumab[50-51,96,194-195] , with reported DCRs of 75–96% for trastuzumab in combination with chemotherapy[51,96] .

SUPPORTING DATA

In the Phase 2a MyPathway basket trial, treatment with trastuzumab plus pertuzumab for patients with non-small cell lung cancer (NSCLC) elicited an ORR of 13% (2/16, 2 PRs) for patients with ERBB2 amplification or overexpression and 21% (3/14, 3 PRs) for patients with ERBB2 mutations[196]. A Phase 2 trial of trastuzumab plus docetaxel for patients with HER2 overexpressing NSCLC did not report any responses among patients treated with trastuzumab monotherapy (n=4) or combination therapy (n=13)[197]. Another Phase 2 study for patients with NSCLC reported an ORR of 23% (7/30) following treatment with trastuzumab and 32% (11/34) with trastuzumab and paclitaxel; responses were seen among HER2+ and HER2- patients[198]. A patient with HER2+ lung adenocarcinoma that harbored an ERBB2 G776L mutation experienced a PR following treatment with trastuzumab and paclitaxel[49]. In a retrospective analysis of patients with NSCLC harboring ERBB2 exon 20 insertion mutations, disease control was reported for 93% of patients (13/14) treated with trastuzumab in combination with chemotherapy[51].

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
G776>VC

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. This combination is available in the EU to treat patients with HER2-positive (HER2+) metastatic or unresectable 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[53,196,199-203] .

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)[196,204] . 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[205].

Trastuzumab deruxtecan

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Trastuzumab deruxtecan is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface and delivers the cytotoxic payload deruxtecan, which inhibits DNA topoisomerase I to induce DNA damage. Trastuzumab deruxtecan is available in the EU to treat patients with HER2+ breast cancer and gastric or gastroesophageal junction (GEJ) adenocarcinoma. It is also approved for patients with HER2-low advanced breast cancer who have previously been treated with chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer (NSCLC)[59,206] , ERBB2 missense or exon 20 insertion mutations may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

The Phase 2 DESTINY-Lung01 study of single-agent fam-trastuzumab deruxtecan for patients with advanced metastatic ERBB2-altered non-small cell lung cancer (NSCLC) predominantly harboring exon 20 insertions reported an ORR of 55% (50/91), median duration of response of 9.3 months, median PFS of 8.2 months, and mOS of 17.8 months[59]. In a similar setting evaluating fam-trastuzumab deruxtecan at a slightly lower dose, the Phase 2 DESTINY-Lung-02 study reported similar efficacy with ORRs of 58% (30/52) and 43% (12/28) and median durations of response of 8.7 months and 5.9 months at doses of 5.4 mg/kg and 6.4 mg/kg, respectively[207]. Fam-trastuzumab deruxtecan achieved a 40% ORR (2/5 PRs) and 80% DCR (4/5) in a retrospective analysis for patients with metastatic ERBB2-mutated/EGFR wildtype NSCLC; patients treated with other trastuzumab regimens had significantly larger tumor sizes (p=0.045)[208].

Trastuzumab emtansine

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, inhibiting HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is available in the EU to treat patients with HER2-positive (HER2+) advanced breast carcinoma and disease progression on prior therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1[56,209-224] . Patients with NSCLC and various ERBB2 exon 20 insertion mutations have benefited from T-DM1[91,212,225] .

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)[211]. 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)[212]. 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[96,225] .

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. 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. Therapies listed in this report may not be complete and/or exhaustive. In particular, the listed therapies are limited to EMA or nationally approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be EMA or nationally 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 EMA or an EU Member State nationally. There may also be other treatment modalities available than pharmaceutical drug products.

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
G776>VC

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 G776>VC or P780_Y781insGSP is associated with improved PFS on afatinib, compared with other ERBB2 mutations or exon 20 insertions. In addition, clinical data suggests reduced sensitivity of ERBB2 G776>VC to dacomitinib. Investigational agents such as poziotinib and pyrotinib, or ERBB2-targeted antibodies such as trastuzumab and T-DM1, may be more effective.

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, RAFs, NRAS

LOCATIONS: Manchester (United Kingdom), Glasgow (United Kingdom), London (United Kingdom), Gent (Belgium), Lille (France), Bruxelles (Belgium), Charleroi (Belgium), Mönchengladbach (Germany), Essen (Germany), Hamburg (Germany)

NCT04042701

PHASE 1

DS8201a and Pembrolizumab in Participants With Locally Advanced/Metastatic Breast or Non-Small Cell Lung Cancer

TARGETS
PD-1, ERBB2

LOCATIONS: Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Créteil (France), Poitiers (France), Marsielle (France), Bordeaux (France), Toulouse (France), Marseille (France)

NCT05048797

PHASE 3

A Study to Investigate the Efficacy and Safety of Trastuzumab Deruxtecan as the First Treatment Option for Unresectable, Locally Advanced/Metastatic Non-Small Cell Lung Cancer With HER2 Mutations

TARGETS
PD-1, ERBB2

LOCATIONS: Amsterdam (Netherlands), Groningen (Netherlands), Gent (Belgium), Nijmegen (Netherlands), Leuven (Belgium), Hasselt (Belgium), Oldenburg (Germany), Vejle (Denmark), Köln (Germany), Villejuif Cedex (France)

NCT04579380

PHASE 2

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

TARGETS
ERBB2, ER

LOCATIONS: London (United Kingdom), Sutton (United Kingdom), Amsterdam (Netherlands), Kortrijk (Belgium), Edegem (Belgium), Mechelen (Belgium), Brussels (Belgium), Charleroi (Belgium), Liege (Belgium), Berlin (Germany)

NCT03974022

PHASE 1/2

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

TARGETS
ERBB2, EGFR

LOCATIONS: Paris (France), Villejuif (France), Saint-Herblain (France), Poitiers (France), Dijon (France), Milano (Italy), Montpellier (France), Marseille (France), Reggio Emilia (Italy), Ravenna (Italy)

NCT04886804

PHASE 1

A Study to Test Different Doses of BI 1810631 in People With Different Types of Advanced Cancer (Solid Tumours With Changes in the HER2 Gene)

TARGETS
ERBB2

LOCATIONS: Amsterdam (Netherlands), Texas, California, Chiba, Kashiwa (Japan), Tokyo, Chuo-ku (Japan), Guangzhou (China)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

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

LOCATIONS: Stavanger (Norway), Kristiansand (Norway), Bergen (Norway), Skien (Norway), Førde (Norway), Trondheim (Norway), Drammen (Norway), Fredrikstad (Norway), Oslo (Norway), Hamar (Norway)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

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

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

NCT05159245

PHASE 2

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

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

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

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

LOCATIONS: Maine

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.

ARID1A
Q1334_R1335insQ

ASXL1
S79G

ERBB2
Q97H

IRS2
A512T

RB1
I172_Y173insELI

TBX3
A350S

WT1
K454R

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 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)	***KRAS***

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.

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 GENOMIC SIGNATURES

Microsatellite (MS) status
Blood Tumor Mutational Burden (bTMB)
ctDNA Tumor Fraction

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.

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 ctDNA 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 ctDNA 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:* The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

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. ctDNA tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The ctDNA tumor fraction estimate integrates multiple distinct genomic features, including modeled aneuploidy and the observed allele frequencies of somatic short variants and rearrangements.
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 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

Genomic signatures and gene alterations 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 genomic signature or gene alteration. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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.

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.6.0

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