FOUNDATIONONE®LIQUID CDx

PATIENT
Sample, Jane

TUMOR TYPE
Lung adenocarcinoma

REPORT DATE
01 June 2020

ORDERED TEST #
ORD-XXXXXXX-XX

PATIENT

DISEASE Lung adenocarcinoma
NAME Not Given
DATE OF BIRTH Not Given
SEX Not Given
MEDICAL RECORD # Not Given

PHYSICIAN

ORDERING PHYSICIAN Not Given
MEDICAL FACILITY Not Given
ADDITIONAL RECIPIENT Not Given
MEDICAL FACILITY ID Not Given
PATHOLOGIST Not Given

SPECIMEN

SPECIMEN ID Not Given
SPECIMEN TYPE Not Given
DATE OF COLLECTION Not Given
SPECIMEN RECEIVED Not Given

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
EGFR exon 19 deletion (L747_A750>P)	IRESSA® (gefitinib) TAGRISSO® (osimertinib) TARCEVA® (erlotinib)

Other Short Variants Identified

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product.
See *professional services* section for information on the alterations listed in this section as well as any additional detected copy number alterations, gene rearrangements, or biomarkers.

OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

TP53 C242G #

#Refer to appendix for limitation statement relating to detection of alterations in ASXL1, ATM, CBL, CHEK2, DNMT3A, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2, TP53, and U2AF1.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

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

Electronically signed by Julia A. Elvin, M.D., Ph.D. | 01 June 2020
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COUNTRY CODE
US

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Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

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SPECIMEN

SPECIMEN ID Not Given
SPECIMEN TYPE Blood
DATE OF COLLECTION Not Given
SPECIMEN RECEIVED Not Given

Biomarker Findings

Blood Tumor Mutational Burden - 5 Muts/Mb
Microsatellite status - Cannot Be Determined
Tumor Fraction - 13%

Genomic Findings

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

EGFR exon 19 deletion (L747_A750>P)
TP53 C242G

7 Therapies with Clinical Benefit
0 Therapies with Lack of Response
10 Clinical Trials

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 5 Muts/Mb	No therapies or clinical trials. see Biomarker Findings section
Microsatellite status - Cannot Be Determined	**Unable to determine Microsatellite status due insufficient evidence of genomic instability.**
Tumor Fraction - 13%	**Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.**

GENOMIC FINDINGS	MAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
***EGFR* -** exon 19 deletion (L747_A750>P)	0.20%	Afatinib	1	none
		Dacomitinib	1	
		Erlotinib	1	
		Gefitinib	1	
		Osimertinib	1	

10 Trials see p. 11

NCCN Category

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

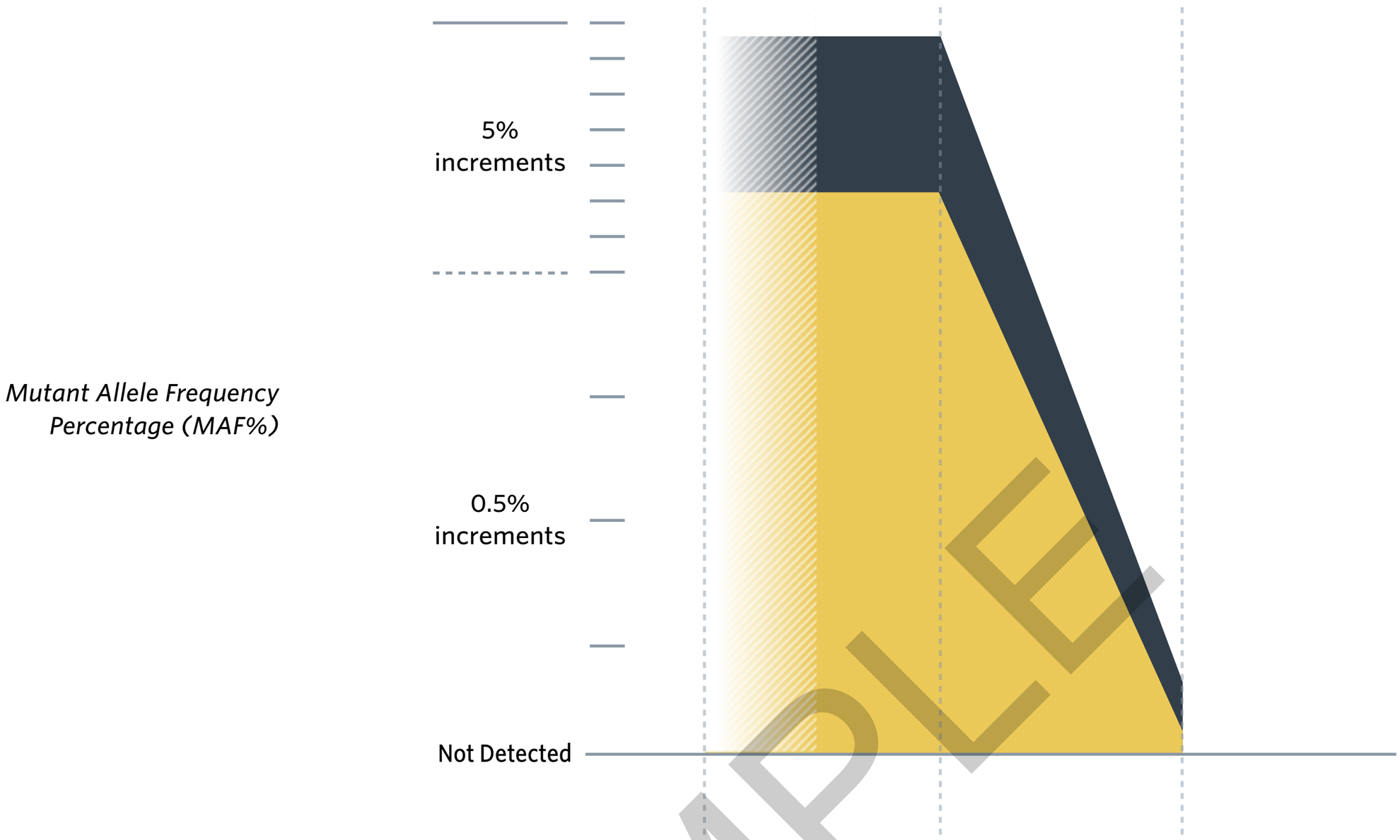
For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

TP53 - C242G p. 7

IMPORTANT NOTE Genomic alterations detected may be associated with activity of certain FDA-approved drugs, however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the clinical 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. In the appropriate clinical context, germline testing of APC, BRCA1, BRCA2, BRIP1, MEN1, MLH1, MSH2, MSH6, MUTYH, NF2, PALB2, PMS2, PTEN, RAD51C, RAD51D, RB1, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TGFBR2, TP53, TSC1, TSC2, VHL, and WT1 is recommended.

Mutant Allele Frequency is not applicable for copy number alterations.

ORDERED TEST # ORD-XXXXXXX-XX



HISTORIC PATIENT FINDINGS		FoundationOne® 25 Feb 2017 ORDXXXXX-XXXX-XXXX	FoundationOne®Liquid 7 Apr 2017 ORDXXXXX-XXXX-XXXX MAF%	FoundationOne®Liquid CDx 01 Jun 2020 ORDXXXXX-XXXX-XXXX MAF%	CHANGE FROM PREV.
Tumor Mutational Burden		Cannot Be Determined	Not Tested	Not Tested	—
Blood Tumor Mutational Burden		Not Tested	Not Tested	5 Mut/Mb	—
Microsatellite status		Cannot Be Determined	Cannot Be Determined	Cannot Be Determined	—
Tumor Fraction		Not Tested	Not Tested	13.0%	—
EGFR	● exon 19 deletion (L747_A750>P)	Detected	23.0%	0.20%	-22.8%
TP53	● C242G	Detected	12.5%	0.10%	-12.4%

IMPORTANT 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.

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ORDERED TEST # ORD-XXXXXXX-XX

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 (MAF% is not applicable)
MAF% = mutant allele frequency percentage
Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

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BIOMARKER

Blood Tumor Mutational Burden

RESULT

5 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in NSCLC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1 (Socinski et al., 2019 ESMO Abstract LBA83, Gandara et al., 2018; 30082870, Wang et al., 2019; 30816954) and anti-PD-1 (Aggarwal et al., 2020; 32102950, Peters et al., 2019; AACR Abstract CT074) therapies. A retrospective analysis of 2 large randomized trials demonstrated patients with NSCLC and a bTMB ≥10 Muts/Mb achieved greater clinical benefit following treatment with atezolizumab than those with bTMB <10 Muts/Mb (Gandara et al., 2018; 30082870); similar results have been reported in additional clinical trials using either PD-1 or PD-L1 inhibitors and at higher bTMB cutpoints for patients with NSCLC (Socinski et al., 2019 ESMO Abstract LBA83, Aggarwal et al. 2020; 32102950, Rizvi et al., 2019; ASCO Abstract 9016). In a small study, treatment with PD-1 or PD-L1 inhibitors resulted in improved PFS for patients with NSCLC and bTMB ≥6 Muts/Mb as compared to patients with bTMB <6 Muts/Mb (Wang et al., 2019; 30816954).

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb) (Aggarwal et al., 2020; 32102950). Increased bTMB has been associated with longer PFS and OS in patients with NSCLC treated with anti-PD-1 or anti-PD-L1 immunotherapy as compared with patients with lower TMB. Elevated bTMB ≥10 Muts/Mb was associated with longer PFS and OS in patients treated with atezolizumab as compared with patients with lower TMB (Gandara et al., 2018; 30082870, Chen et al., 2019; 31921683), while elevated bTMB ≥16 Muts/Mb was associated with improved PFS and OS in patients with NSCLC treated with pembrolizumab (Aggarwal et al., 2020; 32102950) and elevated bTMB ≥20 Muts/Mb was associated with improved survival in patients with NSCLC treated with durvalumab (Rizvi et al., 2019; ASCO Abstract 9016)

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 (Pfeifer et al., 2005; 15748635, Hill et al., 2013; 23875803) and cigarette smoke in lung cancer (Pfeifer et al., 2002; 12379884, Rizvi et al., 2015; 25765070), treatment with temozolomide-based chemotherapy in glioma (Johnson et al., 2014; 24336570, Choi et al., 2018; 29452419), mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes (Cancer Genome Atlas Research Network, 2013; 23636398, Briggs and Tomlinson, 2013; 23447401, Heitzer and Tomlinson, 2014; 24583393, Cancer Genome Atlas Network, 2012; 22810696, Roberts and Gordenin, 2014; 25568919), and microsatellite instability (MSI) (Cancer Genome Atlas Research Network, 2013; 23636398, Cancer Genome Atlas Network, 2012; 22810696, Roberts and Gordenin, 2014; 25568919). This sample harbors a bTMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents (Socinski et al., 2019 ESMO Abstract LBA83, Gandara et al., 2018; 30082870, Wang et al., 2019; 30816954, Aggarwal et al., 2020; 32102950, Rizvi et al., 2019; ASCO Abstract 9016).

BIOMARKER

Tumor Fraction

RESULT

13%

POTENTIAL TREATMENT STRATEGIES

There are currently no targeted approaches to address specific tumor fraction levels; however, on the basis of emerging clinical evidence, changes in tumor fraction may correlate with treatment duration and clinical response and may be a useful indicator for cancer management (Bronkhorst et al., 2019; 30923679, Raja et al., 2018; 30093454, Hrebien et al., 2019; 30860573; Conteduca et al., 2019; ASCO abstract 5039, Choudhury et al., 2018; 30385733, Goodall et al., 2017; 28450425, Goldberg et al., 2018; 29330207).

FREQUENCY & PROGNOSIS

Detectible ctDNA levels has been reported in a variety of tumor types, with higher tumor fraction levels reported in patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3) (Bettegowda et al., 2014; 24553385). Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer (Lapin et al., 2018; 30400802), Ewing sarcoma and osteosarcoma (Shulman et al., 2018; 30131550), prostate cancer (Choudhury et al., 2018; 30385733, Conteduca et al., 2019; ASCO abstract 5039), breast cancer (Stover et al., 2018; 29298117), leiomyosarcoma (Hemming et al., 2019; 30793095), esophageal cancer (Egyud et al., 2019; 31059681), and colorectal cancer (Fan et al., 2017; 28187169).

FINDING SUMMARY

Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. Tumor cells in most advanced solid tumor types may shed ctDNA through the process of apoptosis or necrosis (Bettegowda et al., 2014; 24553385, Snyder et al., 2016; 26771485, Stroun et al., 2001; 11694251). Tumor fraction has been proposed to be a noninvasive surrogate biomarker of disease burden dynamics. Elevated tumor fraction levels have been associated with inferior prognosis, and therapeutic resistance to treatment in certain tumor types (Choudhury et al., 2018; 30385733, Stover et al., 2018; 29298117, Fan et al., 2017; 28187169), whereas reduced levels have been correlated with tumor shrinkage and improved clinical outcome in patients with non-small cell lung cancer, urothelial cancer, and melanoma treated with immunotherapy (Raja et al., 2018; 30093454, Lipson et al., 2014; 25516806, Goldberg et al., 2018; 29330207).

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GENE
EGFR

ALTERATION
exon 19 deletion (L747_A750>P)

TRANSCRIPT NUMBER
NM_005228

CODING SEQUENCE EFFECT
2238_2248ATTAAGAGAAG>GC

POTENTIAL TREATMENT STRATEGIES

EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib (Rosell et al., 2011; 22285168), gefitinib (Douillard et al., 2014; 24263064), afatinib (Sequist et al., 2013; 23816960), dacomitinib (Mok et al., 2018; 29864379), and osimertinib (Janne et al., 2015; 25923549). Third-generation EGFR inhibitors, such as osimertinib, selectively target mutated EGFR, including EGFR T790M (Janne et al., 2015; 25923549, Soria et al., 2018; 29151359). Osimertinib achieved an ORR of 61% in T790M-positive cases and 21% in T790M-negative cases (Janne et al., 2015; 25923549). Resistance to EGFR inhibition may arise by reactivation of the MAPK pathway, and preclinical evidence suggests that co-targeting EGFR and MAPK signaling may retard the development of acquired resistance to third-generation EGFR inhibitors (Ercan et al., 2012; 22961667, Eberlein et al., 2015; 25870145, Tricker et al., 2015; 26036643). Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin (Thatcher et al., 2015; 26045340, Paz-Ares et al., 2015; 25701171) that has also shown benefit in patients with CRC and melanoma (Elez et al., 2016; 26766738, Kuenen et al., 2010; 20197484). Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy (Shimamura et al., 2005; 16024644, Shimamura et al., 2008; 18632637, Sawai et al., 2008; 18199556, Janne et al., 2015; 25923649). Preclinical studies have reported that EGFR-mutant cells (Shimamura et al., 2005; 16024644, Shimamura et al., 2008; 18632637, Sawai et al., 2008; 18199556), including cells with exon 20 insertions (Xu et al., 2007; 17712310), are sensitive to HSP90 inhibitors. For patients with EGFR exon 19 deletion/ L858R- positive and T790M- negative NSCLC who had previously progressed on first or second generation EGFR TKIs, a Phase 1 study evaluating the HER3-targeted antibody U3-1402 reported tumor reduction in 12 patients with 2 confirmed PRs (2/13) (Janne et al., 2019; ASCO Abstract 9010). Consistent with preclinical data demonstrating that the EGFR inhibitor AZD3759 is capable of penetrating the blood-brain barrier and reducing the volume of brain and leptomeningeal metastases, preliminary results from a Phase 1 trial evaluating single-agent AZD3759 reported a reduction in the volume of brain metastases in 40.0% (8/20) of patients with previously treated NSCLC harboring either EGFR L858R or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs (Ahn et al., 2016; ASCO Abstract 9003, Zeng et al., 2015; 26313252,Yang et al., 2016; 27928026). In a Phase I/II trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54.3% (69/127) for all evaluable patients and 44.4% (8/18, intracranial) for patients with brain metastases (Ahn et al., 2019; ASCO 31587882). The reovirus Reolysin targets cells with activated RAS signaling (Strong et al., 1998; 9628872, Coffey et al., 1998; 9812900, Gong and Mita, 2014; 25019061) and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer (Forsyth et al., 2008; 18253152, Vidal et al., 2008; 18981012, Gollamudi et al., 2010; 19572105, Harrington et al., 2010; 20484020, Comins et al., 2010; 20926400, Lolkema et al., 2011; 21106728, Galanis et al., 2012; 22871663, Karapanagiotou et al., 2012; 22316603, Morris et al., 2013; 22886613). The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear (Villalona-Calero et al., 2015; 26709987, Morris et al., 2016; ASCO Abstract e20512).

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas (Vallee et al., 2013; 23934203, Imielinski et al., 2012; 22980975, Cancer Genome Atlas Research Network., 2014; 25079552) and in 4% of lung squamous cell carcinomas (Cancer Genome Atlas Research Network., 2012; 22960745). EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases (Watzka et al., 2010; 20353893, Liang et al., 2010; 20637128, Grob et al., 2013; 23238037, Park et al., 2012; 22207554, Dobashi et al., 2011; 21040950, Ludovini et al., 2013; 23314677). In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma (Skrzypski et al., 2013; 23870818, Kim et al., 2012; 22419022). In lung adenocarcinoma, EGFR gene amplification was a predictor of poor disease-free survival in all patients and of poor overall survival in patients with EGFR mutations (Lee et al., 2013; 23525704, Oakley and Chiosea, 2011; 21587084). Nuclear expression of EGFR in NSCLC has been reported to associate with higher disease stage, shorter progression-free survival, and shorter overall survival (Traynor et al., 2013; 23628526). However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma (Marks et al., 2008; 18303429) or resected Stage 1 NSCLC (Izar et al., 2013; 23932319).

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide (Ciardiello and Tortora, 2008; 18337605). The EGFR mutation seen here is a deletion in exon 19, encoding a portion of the kinase domain of EGFR; such mutations have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib (Lynch et al., 2004; 15118073, Paez et al., 2004; 15118125, Pao et al., 2004; 15329413), afatinib (Yang et al., 2015; 25589191), osimertinib (Soria et al., 2018; 29151359), and dacomitinib (Wu et al., 2017; 28958502, Mok et al., 2018; 29864379), although limited preclinical data suggest reduced sensitivity to lapatinib (Gilmer et al., 2008; 18199554, Foster et al., 2016; 26996308).

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GENE
TP53

ALTERATION
C242G

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
724T>G

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor AZD1775[61,62,63,64], therapies that reactivate mutant p53 such as APR-246 (Gourley et al., 2016; ASCO Abstract 5571)[65,66,67], or p53 gene therapy and immunotherapeutics such as SGT-53[68,69,70,71,72] and ALT-801 (Hajdenberg et al., 2012; ASCO Abstract e15010). In a Phase 1 study, AZD1775 in combination with gemcitabine, cisplatin, or carboplatin elicited partial response in 10% (17/176) and stable disease in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53-wild-type[73]. Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer (Oza et al., 2015; ASCO Abstract 5506). Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel (Leijen et al., 2015; ASCO Abstract 2507). In a Phase 1b trial in 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% disease control rate (Gourley et al., 2016; ASCO Abstract 5571). In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including two confirmed and one unconfirmed partial responses and two instances of stable disease with significant tumor shrinkage[72]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model[74]. Kevetrin has also been reported to activate p53 in preclinical studies and might be relevant in the context of mutant p53 (Kumar et al., 2012; AACR Abstract 2874). Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer. TP53 mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[8,52,53,54,55,56,57,58]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[59]. 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[60].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[41]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[42,43,44]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[45,46,47,48,49,50]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,00051 to 1:20,00050, and in the appropriate clinical context, germline testing of TP53 is recommended.

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Afatinib

Assay findings association

EGFR

exon 19 deletion (L747_A750>P)

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 treatment of metastatic non-small cell lung cancer (NSCLC) in patients with EGFR exon 19 deletions or exon 21 (L858R) missense mutations.

GENE ASSOCIATION

EGFR activating mutations or amplification may indicate sensitivity to afatinib. In Phase 2 studies of afatinib, patients with EGFR-amplified NSCLC achieved an objective response rate of 20% (5/25) and a disease-control rate of 64% (16/25) (Cappuzzo et al., 2015; 25514804), and 2/5 patients with EGFR amplification in other solid tumors experienced stable disease (Kwak et al., 2013; 23775486).

SUPPORTING DATA

Phase 3 clinical trials have demonstrated that treatment with afatinib, compared to chemotherapy, leads to significantly increased progression-free survival for patients with EGFR-mutant NSCLC (Sequist et al., 2013; 23816960, Wu et al., 2014; 24439929), and increased overall survival (OS) for patients with EGFR exon 19 alterations specifically (Yang et al., 2015; 25589191). A Phase 3 trial comparing afatinib with erlotinib as second-line therapies for advanced lung squamous cell carcinoma reported significantly higher OS (7.9 months vs. 6.8 months) and disease control rate (DCR) (51% vs. 40%) for patients treated with afatinib (Soria et al., 2015; 26156651). Phase 2/3 studies of afatinib treatment for patients with erlotinib- or gefitinib-resistant NSCLC have generally reported partial responses (PRs) of only 7-9% (Miller et al., 2012; 22452896, Chen et al., 2013; 23664448, Katakami et al., 2013; 23816963, Landi et al., 2014; 25242668, De Greve et al., 2015; 25682316, Yang et al., 2015; 26051236), and DCRs of more than 50% (De Greve et al., 2015; 25682316); in particular, disease control was achieved for 2/2 patients with EGFR-amplified NSCLC (De Greve et al., 2015; 25682316) and 9/14 patients with T790M-positive NSCLC (Yang et al., 2015; 26051236). The T790M mutation has been implicated in reduced response to afatinib (Wu et al., 2016; 26862733, Landi et al., 2014; 25242668, Kim et al., 2012; 22228822), with a secondary T790M mutation reported in 48% (20/42) of patients with afatinib-resistant lung adenocarcinoma (Wu et al., 2016; 26862733). The combination of afatinib with cetuximab resulted in a higher response rate (29%) for patients with erlotinib- or gefitinib-resistant disease (Janjigian et al., 2014; 25074459), including T790M-positive cases (Janjigian et al., 2014; 25074459, Ribeiro Gomes and Cruz, 2015; 26056478), although adverse reactions may be a concern with this combination (Castellanos et al., 2015; 25842367). Upon progression on afatinib, further benefit has been reported from combination treatment with afatinib and paclitaxel (Schuler et al., 2016; 26646759).

Dacomitinib

Assay findings association

EGFR

exon 19 deletion (L747_A750>P)

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical (Wu et al., 2017; 28958502, Mok et al., 2018; 29864379, Necchi et al., 2018; 28921872) and preclinical (Zhu et al., 2014; 24658109, Zahonero et al., 2015; 259761) data, EGFR amplification or activating mutation may indicate sensitivity to dacomitinib. Patients with untreated advanced NSCLC and EGFR exon 19 deletions achieved an ORR of 76% (Wu et al., 2017; 28958502) and a median OS of 34.1 months with dacomitinib (Mok et al., 2018; 29864379).

SUPPORTING DATA

A randomized Phase 3 trial in patients with NSCLC with activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS, 34.1 vs. 26.8 months, HR=0.760; median PFS, 14.7 vs. 9.2 months, HR=0.59) (Mok et al., 2018; 2986437, Wu et al., 2017; 28958502); median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen (Wu et al., 2018; WCLC abstract MA26.11). A pooled subgroup analysis of patients with NSCLC with activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (median PFS, 14.6 vs, 9.6 months, HR=0.717; median OS, 26.6 vs, 23.2 months, HR=0.737)(Ramalingam et al., 2016; 26768165). Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies (Yu et al., 2017; 29191595, Reckamp et al., 2014; 24501009, Janne et al., 2011; 21220471). A Phase 2 study of dacomitinib in patients with NSCLC who had been previously treated with chemotherapy or erlotinib and were not selected for EGFR mutations reported an ORR of 4.5% (3/66) (Reckamp et al., 2014; 24501009). In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC (Janne et al., 2016; 26899759).

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Erlotinib

Assay findings association

EGFR

exon 19 deletion (L747_A750>P)

AREAS OF THERAPEUTIC USE

Erlotinib is a small molecule inhibitor of EGFR. It is FDA approved for the treatment of non-small cell lung cancer (NSCLC) and pancreatic cancer.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. In a prospective study of advanced NSCLC treated with gefitinib (n=102), EGFR copy gain was significantly associated with improved survival [hazard ratio (HR)=0.44] (Cappuzzo et al., 2005; 15870435). Several meta-analyses spanning 14 to 20 studies of patients with advanced NSCLC receiving single-agent erlotinib or gefitinib (n=1725 to 1854) reported the association of increased EGFR copy number with improved overall survival (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11) (Zhang et al., 2017; 27664271, Dahabreh et al., 2011; 20826716, Dahabreh et al., 2010; 20028749).

SUPPORTING DATA

The initial approval of erlotinib in NSCLC was based on the BR.21 Phase 3 randomized trial demonstrating prolonged overall survival for unselected patients with NSCLC treated with erlotinib compared with standard chemotherapy (Shepherd et al., 2005; 16014882). Furthermore, several randomized Phase 3 trials have shown a significant improvement in response and progression-free survival for erlotinib compared with combination chemotherapy in patients with known EGFR mutations. This includes the EURTAC trial of erlotinib versus platinum-based chemotherapy as first-line treatments (Rosell et al., 2011; 22285168) and the SATURN trial of erlotinib as maintenance therapy following first-line platinum-based chemotherapy (Cappuzzo et al., 2010; 20493771). On the other hand, the efficacy of erlotinib for patients lacking the common EGFR activating alterations (exon 19 deletion or L858R mutation) may be regimen-dependent. For patients with NSCLC and wild-type EGFR, chemotherapy was found to be more effective than erlotinib as first-, second-, or third-line treatment (Garassino et al., 2013; 23883922, Kawaguchi et al., 2014; 24841974, Liu et al., 2016; 26206590). However, as maintenance therapy, erlotinib reduced risk for progression compared with placebo by 19% (hazard ratio = 0.81) (Liu et al., 2016; 26206590). The single-arm, Phase IV TRUST trial for genomically unselected patients with advanced NSCLC who failed on, or were unsuitable for, chemotherapy or who were ineligible for erlotinib clinical trials reported a disease control rate of 69% (Reck et al., 2010; 20736854).

Gefitinib

Assay findings association

EGFR

exon 19 deletion (L747_A750>P)

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and progression-free survival for patients with EGFR-mutated NSCLC treated with gefitinib, compared to chemotherapy (Han et al., 2012; 22370314, Maemondo et al., 2010; 20573926, Mitsudomi et al., 2010; 20022809, Mok et al., 2009; 19692680, Petrelli et al., 2011; 22056888, Qi et al., 2015; 25329826, Zhao et al., 2015; 25546556).

SUPPORTING DATA

Gefitinib achieved an objective response rate of 69.8% and an overall survival of 19.2 months as first-line treatment of Caucasian patients with non-small cell lung carcinoma (NSCLC) and EGFR sensitizing mutations, which were mostly EGFR exon 19 deletions and EGFR L858R (Douillard et al., 2014; 24263064). In the retrospective analysis of a Phase 3 study in East Asia, gefitinib increased progression-free survival (PFS) in a subgroup of patients with EGFR mutation-positive NSCLC as compared with carboplatin/paclitaxel doublet chemotherapy (hazard ratio for progression = 0.48) (Fukuoka et al., 2011; 21670455, Mok et al., 2009; 19692680). In a Phase 2 study, addition of pemetrexed to gefitinib improved median PFS (15.8 months) compared to treatment with gefitinib alone (10.9 months) in East Asian patients with treatment-naïve, advanced non-squamous NSCLC and activating EGFR mutations (Cheng et al., 2016; 27507876). A retrospective analysis of patients with advanced NSCLC of Asian descent receiving first-line gefitinib therapy reported that patients with EGFR exon 19 mutations experienced longer median PFS (10.9 months) compared to patients with EGFR mutations in exons 18 (7.9 months), 20 (1.2 months), 21 (7.7 months), or double mutations (5.7 months); however, no differences in overall survival were seen between EGFR mutations (Sutiman et al., 2017; 27908825). In a Phase 1 study for treatment-naïve patients with NSCLC, best objective response rates of 78% (7/9) were observed in patients treated with combination gefitinib and the PD-L1 inhibitor durvalumab as first-line treatment and of 80% (8/10) in those treated with the combination subsequent to gefitinib monotherapy (Gibbons et al., 2016; 27198414).

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Osimertinib

Assay findings association

EGFR

exon 19 deletion (L747_A750>P)

AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR tyrosine kinase inhibitor (TKI) that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved to treat patients with metastatic EGFR T790M-positive non-small cell lung cancer (NSCLC) and disease progression on or after EGFR TKI therapy.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations and/or the EGFR T790M mutation may predict sensitivity to osimertinib22,179. T790M-positive patients showed higher response rates than T790M- negative cases in a Phase 1 study for patients with acquired EGFR TKI resistance (61% vs. 21%)22. Although tumors with EGFR amplification may not be sensitive to osimertinib, which selectively targets mutated EGFR, preclinical data indicate sensitivity of various activating EGFR alterations to osimertinib.[179]

SUPPORTING DATA

Osimertinib has been studied primarily for the treatment of EGFR-mutated NSCLC. In Phase 3 study for patients with EGFR T790M-positive advanced NSCLC who had progressed on EGFR TKI therapy, osimertinib compared with combination platinum therapy led to longer median progression-free survival (PFS) (10.1 months vs. 4.4 months), including for patients with metastases to the central nervous system (8.5 months vs. 4.2 months). An objective response rate (ORR) of 71% was achieved with osimertinib compared to 31% with combination platinum therapy (Mok et al., 2016; DOI: 10.1056/NEJMoa1612674). A Phase 2 study of osimertinib reported an ORR of 70% with a median duration of response of 11.4 months and a median PFS of 9.9 months for T790M-positive NSCLC patients with disease progression after previous EGFR TKI therapy180. A Phase 1 trial demonstrated similar outcomes for T790M-positive patients (Yang et al., 2016; ELCC Abstract LBA2_PR), but reported an ORR of 21% and median PFS of 2.8 months for T790M-negative cases with acquired EGFR TKI resistance22. Treatment-naïve patients with EGFR-mutated NSCLC achieved an ORR of 77% (46/60 overall, 20/30 with 80 mg, 26/30 with 160 mg), a stable disease rate of 20% (12/60), and a median PFS of 19.3 months (Ramalingam et al., 2016; ELCC Abstract LBA1_PR). A Phase 1b study combined osimertinib with the investigational immunotherapy durvalumab, MEK inhibitor selumetinib, or MET inhibitor savolitinib, and observed partial responses (PR) for each of the combinations (9/14 PR with durvalumab, 9/23 PR with selumetinib, 6/11 PR with savolitinib) (Ramalingam et al., 2015; ASCO Abstract 2509). Osimertinib is being compared with erlotinib or gefitinib as first-line treatment for EGFR-mutant NSCLC (NCT02296125).

IMPORTANT NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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ORDERED TEST # ORD-XXXXXXX-XX

CLINICAL TRIALS

IMPORTANT NOTE Clinical trials are ordered by gene and prioritized by (in order of descending priority): 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. 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.

GENE
EGFR

ALTERATION
exon 19 deletion (L747_A750>P)

RATIONALE
Activating mutations in EGFR have been shown to confer sensitivity to EGFR inhibitors. However, the presence of the T790M resistance mutation suggests that some inhibitors will be ineffective. Other agents, including irreversible EGFR inhibitors and HSP90 inhibitors, may be relevant, although tumors with EGFR amplification may not be sensitive to third-generation EGFR inhibitors with high selectivity for mutated EGFR such as rociletinib. Examples of clinical trials that may be appropriate for this patient are listed below.

NCT02193282

PHASE 3

Randomized Double Blind Placebo Controlled Study of Erlotinib or Placebo in Patients With Completely Resected Epidermal Growth Factor Receptor (EGFR) Mutant Non-Small Cell Lung Cancer (NSCLC)

TARGETS
EGFR

LOCATIONS: Kentucky, Tennessee, New Jersey, Alaska, Delaware, North Dakota, Montana, Ohio, Rhode Island, Maine

NCT02438722

PHASE 2 / 3

A Randomized Phase II/III Trial of Afatinib Plus Cetuximab Versus Afatinib Alone in Treatment-Naive Patients With Advanced, EGFR Mutation Positive Non-small Cell Lung Cancer (NSCLC)

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Vermont, Kentucky, New York, Mississippi, Idaho, Iowa, New Jersey, Massachusetts, Florida, Indiana,

NCT02511106

PHASE 3

A Phase III, Double-blind, Randomized, Placebo-controlled Multi-centre, Study to Assess the Efficacy and Safety of AZD9291 Versus Placebo, in Patients With Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy (ADAURA).

TARGETS
EGFR

LOCATIONS: Maryland, Guangzhou (China), Rio Grande do Sul (Brazil), Beer-Sheva (Israel), Hoofddorp (Netherlands), Vinnytsia (Ukraine), Nanjing (China), Taichung (Taiwan), Hamburg (Germany), Poznan (Poland),

NCT02411448

PHASE 3

A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination With Ramucirumab or Placebo in Previously Untreated Patients With EGFR Mutation- Positive Metastatic Non-Small Cell Lung Cancer

TARGETS
EGFR, VEGFR2

LOCATIONS: Pordenone (Italy), Jinju (Korea, Republic of), Pok Fu Lam (Hong Kong), Texas, Chemnitz (Germany), Kaohsiung City (Taiwan), Poitiers (France), Hyogo (Japan), Dongjak-gu (Korea, Republic of), Taichung (Taiwan), Osaka (Japan),

NCT02693535

PHASE 2

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
ABL, CDK4, PARP, EGFR, DDR2, PDGFRs, VEGFRs, ROS1, CSF1R, ERBB2, PD-1, ERBB3, MEK, RAF1, KIT, AXL, SMO, TRKC, mTOR, TRKA, MET, ALK, BRAF, RET, SRC, FLT3, CDK6

LOCATIONS: North Dakota, Pennsylvania, Washington, Illinois, Georgia, Arizona, Utah, North Carolina, Oklahoma, South Dakota,

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ORDERED TEST # ORD-XXXXXXX-XX

CLINICAL TRIALS

NCT02795156

PHASE 2

Phase II Study to Evaluate the Activity of Commercially Available Molecularly Matched Targeted Therapies in Selected Tumor Types Based on Genomic Alterations

TARGETS
EGFR, BRAF, RET, ERBB2, RAF1, KIT, PDGFRs, VEGFRs, ERBB4

LOCATIONS: Tennessee, Colorado, Florida, Missouri

NCT02716116

PHASE 1 / 2

A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor AP32788 in Non-Small Cell Lung Cancer

TARGETS
EGFR, ERBB2

LOCATIONS: New York, California, Tennessee, Massachusetts, Colorado, Virginia

NCT02099058

PHASE 1

A Multicenter, Phase 1/1b, Open-Label, Dose-Escalation Study of ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors

TARGETS
EGFR, MET, PD-1, VEGFA

LOCATIONS: California, Colorado, Illinois, Massachusetts, Michigan, Missouri, North Carolina, Tennessee, Texas, Virginia,

NCT02491775

N / A

Genomic Landscape of EGFR Mutant NSCLC Prior to Afatinib and at the Time of Disease Progression Following Afatinib

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Missouri

NCT02451553

PHASE 1

Phase I/IB Multi-center Study of Irreversible EGFR/HER2 Tyrosine Kinase Inhibitor Afatinib (BIBW 2992) in Combination With Capecitabine for Advanced Solid Tumors and Pancretico-Biliary Cancers

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Indiana, Washington

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

AKT3
E132D

EP300
S12L, S24L, and S26F

IRS2
M543L and R1286Q

LRP1B
C1199F

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INTENDED USE

FoundationOne Liquid CDx is a qualitative next generation sequencing based *in vitro* diagnostic test that uses targeted high throughput hybridization-based capture technology to detect and report substitutions, insertions and deletions (indels) in 311 genes, including rearrangements and copy number losses only in *BRCA1* and *BRCA2*. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood of cancer patients collected in FoundationOne Liquid CDx cfDNA blood collection tubes included in the FoundationOne Liquid CDx Blood Sample Collection Kit. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx is intended to provide tumor mutation profiling for substitutions and indels to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

A negative result from a plasma specimen does not mean that the patient's tumor is negative for genomic findings. Patients who are negative for the mutations listed in Table 1 should be reflexed to routine biopsy and their tumor mutation status confirmed using an FDA-approved tumor tissue test, if available.

Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

FoundationOne Liquid CDx is a single-site assay performed at Foundation Medicine, Inc. in Cambridge, MA.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

TUMOR TYPE	BIOMARKER(S) DETECTED	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* Exon 19 deletions and *EGFR* Exon 21 L858R alteration	IRESSA® (gefitinib) TAGRISSO® (osimertinib) TARCEVA® (erlotinib)
Prostate cancer	*BRCA1, BRCA2* alterations	RUBRACA® (rucaparib)

TEST PRINCIPLE

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. All coding exons of 309 genes are targeted; select intronic or non-coding regions are targeted in *BRCA1* and *BRCA2*. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a custom analysis pipeline designed to detect genomic alterations, including base substitutions and indels in 311 genes, and copy number variants and genomic rearrangements in *BRCA1* and *BRCA2*. A subset of targeted regions in 75 genes is baited for increased sensitivity.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/F1LCDx

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. Genomic findings other than those listed in Table 1 of the intended use are not prescriptive or conclusive for labeled use of any specific therapeutic product.
4. A negative result does not rule out the presence of a mutation in the patient's tumor.
5. 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.
6. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.
7. 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*.
8. The false positive rate of this test was evaluated in healthy donors. The detection rate for unique short variants in apparently healthy patients is 0.82%. Across 30,622 short variants, 58 variants had a detection rate of greater than 5%.
9. The analytical accuracy for the FoundationOne Liquid CDx assay has not been demonstrated in all genes.
10. The precision of FoundationOne Liquid CDx was only confirmed for select variants at the limit of detection.
11. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
12. A complete assessment of the impact of cfDNA blood collection tube lot-to-lot variability on the performance of the test has not been evaluated.
13. The test is not intended to provide information on cancer predisposition.
14. *BRCA1/BRCA2* homozygous deletions and rearrangements were not adequately represented in all analytical studies.
15. Performance has not been validated for cfDNA input below the specified minimum input.

LEVEL 1: COMPANION DIAGNOSTICS (CDx)

Clinical evidence should be presented from a prospectively designed clinical trial. Results can also be presented from a retrospective clinical bridging study demonstrating that the clinical endpoints are preserved using plasma samples in trials where enrollment was based on tissue test results. For follow-on markers, a clinical concordance study demonstrating non-inferiority to the original FDA-approved cfDNA-based companion diagnostic device (refer to Li, Meijuan. Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External Concordance Study. *Statistics in Biopharmaceutical Research*. 8: 35-363, 2016) is required. In addition to the clinical validation, analytical validation for each specific Level 1 CDx biomarker should be presented.

LEVEL 2: cfDNA BIOMARKERS WITH STRONG EVIDENCE OF CLINICAL SIGNIFICANCE IN cfDNA

For a Level 2 claim of cfDNA biomarkers with strong evidence of clinical significance, clinical validation needs to be from evidence presented with FDA-approved liquid biopsy companion diagnostic biomarkers for the specific tumor type at the biomarker or variant level. Such claims should also be supported by analytical performance for each biomarker from at least LoD, precision/reproducibility, and LoD studies.

LEVEL 3A: BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE IN TISSUE SUPPORTED BY STRONG ANALYTICAL VALIDATION USING cfDNA AND CONCORDANCE BETWEEN cfDNA AND TISSUE

Clinical evidence can be provided from tissue-based companion diagnostics. This should also be supported by analytical validation (LoD, precision, analytical accuracy, and concordance study to a tissue-based test) for the specific tumor type at the biomarker or variant level, using a representative approach for SNVs and indels. Evidence evaluating concordance between cfDNA- and tissue-samples for FDA-approved tissue markers should be demonstrated using an FDA-approved tissue test or a validated tissue test.

LEVEL 3B: BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE IN TISSUE SUPPORTED BY ANALYTICAL VALIDATION USING cfDNA

Clinical evidence can be provided from tissue-based companion diagnostics, with analytical validity supported by a representative approach for SNVs and indels from key analytical studies (such as LoD, accuracy, and precision).

LEVEL 4: OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Biomarkers not categorized into Levels 1, 2, or 3 can be included under Level 4 for informational purposes or to be used to direct patients toward clinical trials for which they may be eligible. Such claims can be supported by clinical rationale for inclusion in the panel. Such rationale could also include peer-reviewed publications for genes/variants in tissue, variant information from well-curated public databases, or *in vitro* pre-clinical models. Analytical validation should be supported by a representative approach for SNVs and indels from key analytical studies (such as LoD, accuracy, and precision).

A FLUID APPROACH TO REPORTING LEVELS

As additional information becomes available, findings may move in accordance with the above descriptions.

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APPENDIX Genes assayed in FoundationOne®Liquid CDx

As part of its FDA-approved intended use, the FoundationOne Liquid CDx assay interrogates 311 genes, including 309 genes with complete exonic (coding) coverage and 2 genes with only select non-coding coverage (indicated with an *). Select genes and select exons (indicated in bold) are captured with increased sensitivity.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29**	*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*	***BRAF*** **Exons 11-18**	***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*	*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***	*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**	***EZH2*** **Exons 4, 16, 17, 18**
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	***FGFR1***	***FGFR2***	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18**
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**	*KLHL6*
KMT2A (MLL)	*KMT2D* (MLL2)	***KRAS***	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*

ORDERED TEST # ORD-XXXXXXX-XX

APPENDIX — Genes assayed in FoundationOne®Liquid CDx

As part of its FDA-approved intended use, the FoundationOne Liquid CDx assay interrogates 311 genes, including 309 genes with complete exonic (coding) coverage and 2 genes with only select non-coding coverage (indicated with an *). Select genes and select exons (indicated in bold) are captured with increased sensitivity.

MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	***MET***	*MITF*	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	***MYC***	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**
NBN	***NF1***	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1 **Exons 4-6, 8, 10**	***NRAS*** **Exons 2, 3**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15**	*NTRK2*	***NTRK3*** **Exons 16, 17**	*P2RY8*	***PALB2***
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18**
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**	*RARA*	***RB1***	*RBM10*	*REL*	***RET*** **Exons 11, 13-16**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40**	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	***SMO***	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	***STK11***	*SUFU*
SYK	*TBX3*	*TEK*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*
TNFRSF14	***TP53***	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	***VEGFA***	*VHL*	*WHSC1*
WT1	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*				

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.

PROFESSIONAL SERVICES FINDINGS

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.

RANKING OF ALTERATIONS AND THERAPIES

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

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. 2020. All rights reserved. To view the most recent and complete version of the guideline, 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.

TUMOR MUTATIONAL BURDEN

Tissue 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%.

TUMOR FRACTION

Tumor fraction is the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from observed aneuploid instability in the sample.

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

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)

The content provided as a professional service by Foundation Medicine, Inc., has not been reviewed or approved by the FDA.

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

KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*
MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***
MITF	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*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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