FOUNDATIONONE® LIQUID CDx

PATIENT

TUMOR TYPE
Lung cancer (NOS)

REPORT DATE
03 Jan 2022

COUNTRY CODE
PE

ORDERED TEST #
ORD-1269154-01

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

PATIENT
DISEASE Lung cancer (NOS)
DATE OF BIRTH 21 August 1936
SEX Female
MEDICAL RECORD # Not given

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

SPECIMEN
SPECIMEN ID VRPDW 08/21/1936
SPECIMEN TYPE Blood
DATE OF COLLECTION 17 December 2021
SPECIMEN RECEIVED 23 December 2021

Biomarker Findings

Blood Tumor Mutational Burden - 10 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

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

NF1 **splice site 6705-2A>C, Y863fs*15**
DNMT3A **splice site 1937-1G>A**
NOTCH1 C1101fs*5
TP53 C242S

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Atezolizumab** (p. 9), **Cemiplimab** (p. 10), **Durvalumab** (p. 11), **Nivolumab** (p. 12), **Pembrolizumab** (p. 13)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 16)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A*** **splice site 1937-1G>A** (p. 6)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 10 Muts/Mb	Atezolizumab	1	Avelumab
	Cemiplimab	1	
	Durvalumab	1	
	Nivolumab	1	
	Pembrolizumab	1	
	Dostarlimab		
10 Trials see p. 16			
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**		
Tumor Fraction - Elevated Tumor Fraction Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).**		

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENOMIC FINDINGS		VAF %
NF1 -	splice site 6705-2A>C	0.81%
	Y863fs*15	0.71%

10 Trials see p. 18

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
None	Selumetinib
	Trametinib

☐ *NCCN category*

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

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

DNMT3A - splice site 1937-1G>A p. 6

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

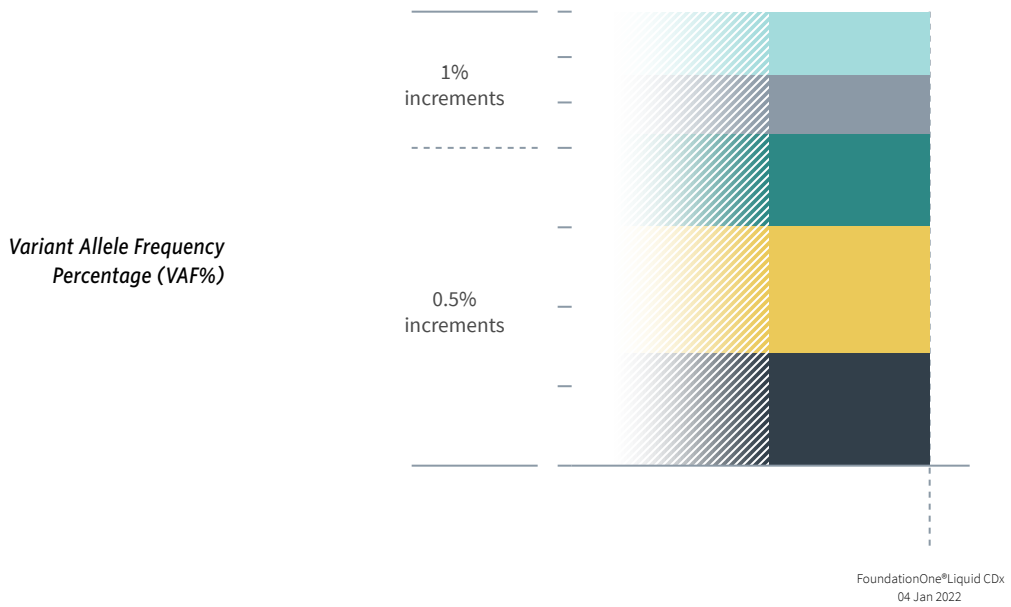
DNMT3A - splice site 1937-1G>A p. 6
NOTCH1 - C1101fs*5 p. 7
TP53 - C242S p. 8

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

Variant Allele Frequency is not applicable for copy number alterations.

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531



HISTORIC PATIENT FINDINGS		ORD-1269154-01 VAF%
Blood Tumor Mutational Burden		10 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
NF1	● Y863fs*15	0.71%
	● splice site 6705-2A>C	0.81%
DNMT3A	● splice site 1937-1G>A	0.80%
NOTCH1	● C1101fs*5	1.4%
TP53	● C242S	1.3%

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

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

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

VAF% = variant allele frequency percentage
Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

BIOMARKER

Blood Tumor Mutational Burden

RESULT
10 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)[3]. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic non-small cell lung cancer (NSCLC) reported that bTMB ≥7 Muts/Mb was associated with shorter PFS (2.8 vs. 4.2 months) and OS (7.4 vs. 11.9 months) compared with bTMB <7 Muts/Mb for patients treated with docetaxel[5]. In one study of advanced NSCLC in China, bTMB ≥6 Muts/Mb was associated with decreased PFS (10 vs. 18 months) and OS (11 vs. 25 months) compared with bTMB <6 Muts/Mb for patients treated with platinum-based chemotherapy[6]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[7]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[8]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[8-9].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[10-11] and cigarette smoke in lung cancer[12-13], treatment with temozolomide-based chemotherapy in glioma[14-15], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[16-20], and microsatellite instability (MSI)[16,19-20]. This sample harbors a bTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3].

BIOMARKER

Tumor Fraction

RESULT
Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[21-26].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[27]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[28], Ewing sarcoma and osteosarcoma[29], prostate cancer[24], breast cancer[30], leiomyosarcoma[31], esophageal cancer[32], colorectal cancer[33], and gastrointestinal cancer[34].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[35], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[36-37].

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
NF1

ALTERATION
splice site 6705-2A>C, Y863fs*15

TRANSCRIPT ID
NM_001042492, NM_001042492

CODING SEQUENCE EFFECT
6705-2A>C, 2586delC

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[38-41], glioma or glioblastoma[41-45], and non-small cell lung cancer[46], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus, based on limited clinical data[47-49] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[50-51]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[52]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[53], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[54].

FREQUENCY & PROGNOSIS

NF1 mutation has been observed in 6.9-11% of lung adenocarcinoma cases[55] and 7.7-11% of lung squamous cell carcinoma cases[56-58]. Published data investigating the prognostic implications of NF1 alteration in lung cancer are limited (PubMed, Feb 2021). However, decreased NF1 expression was reported in 2 lung adenocarcinoma samples after disease progression on first generation EGFR inhibitor and afatinib; neither sample harbored EGFR T790M mutation[59].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[60]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[61]. Alterations such as seen here may disrupt NF1 function or expression[61-70]. The consequences of alterations that may leave the GAP-related domain intact, such as seen here, are unclear; however, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[71-73]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[74-75], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
DNMT3A

ALTERATION
splice site 1937-1G>A

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
1937-1G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2021)[57-58]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2021).

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[76-77]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[78-83]. Alterations such as seen here may disrupt DNMT3A function or expression[84-87].

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[88-93]. 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[88-89]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[94]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[92,95-96]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
NOTCH1

ALTERATION
C1101fs*5

TRANSCRIPT ID
NM_017617

CODING SEQUENCE EFFECT
3300_3301insCAGCGTGTCC

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

NOTCH1 inhibitors and gamma-secretase inhibitors (GSIs) may be potential therapeutic approaches in the case of NOTCH1 activating mutations[97-104]. In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PR in 15% (6/39) and SD in 54% (21/39) of patients with metastatic adenoid cystic carcinoma (ACC) harboring NOTCH activating alterations[105]. Additional responses to AL101 have been reported in a patient with gastroesophageal junction adenocarcinoma harboring multiple NOTCH1 mutations, a patient with T-cell acute lymphoblastic leukemia (T-ALL) harboring a NOTCH1 HD domain mutation, and a patient with ACC harboring a single NOTCH1 mutation[106]. On the basis of clinical data in non-Hodgkin lymphoma, NOTCH1 activating alterations may be associated with sensitivity to the approved PI3K inhibitor copanlisib[107]; this is further supported by limited preclinical data that suggest that NOTCH1 may be a negative regulator of PTEN[108-109]. A study of several cohorts of patients with NSCLC reported an association between deleterious NOTCH mutations (NOTCH1-3 considered as a pooled set) and improved clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors[110]. However, as presence of NOTCH mutation correlates with higher TMB, the independent predictive power of NOTCH alterations is not entirely clear; furthermore, significant associations with improved clinical benefit were not found for mutations in NOTCH1, NOTCH2, or NOTCH3 considered individually, and the study did not delineate clinical associations for different types of NOTCH alterations[110]. Therefore, it is unclear if the alteration seen here would predict efficacy of treatment with an immune checkpoint inhibitor. While activating mutations may be targeted via gamma-secretase inhibitors or PI3K inhibitors, there are no therapies available to address NOTCH1 inactivation, as seen here.

FREQUENCY & PROGNOSIS

Mutation of NOTCH1 has been reported in 4% and 7% of cases, respectively, in the Lung Adenocarcinoma and Lung Squamous Cell Carcinoma TCGA datasets; homozygous loss of NOTCH1 was not reported[55-56]. While NOTCH inactivation or loss in non-small cell lung cancer (NSCLC) has rarely been described in the literature, one study reported that 12% (6/49) of NSCLC samples harbored activating NOTCH1 mutations and another reported that NOTCH1 is overexpressed in NSCLC[111-112]. NOTCH1 mutation has been reported in 10-20% of lung SCC cases in the scientific literature, with both activating and inactivating mutations reported[111,113]. A study of 441 patients with lung adenocarcinoma correlated increased NOTCH activity with poor clinical outcome; HES1 overexpression, a direct target of NOTCH, also correlated with poor overall survival in an independent study of 89 patients with adenocarcinoma[111,114]. NOTCH1 overexpression has been correlated with poor patient survival rates in patients with NSCLC[115]. Activation of the NOTCH1 pathway through cisplatin-induced NOTCH1 expression has been reported to be associated with multidrug resistance in lung adenocarcinoma cells[116].

FINDING SUMMARY

NOTCH1 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or an oncogene[113,117]. Upon binding of membrane-bound ligands, the NOTCH1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex that regulates downstream target genes involved in cell fate determination, proliferation, and apoptosis[118-119]. NOTCH1 alterations that disrupt ligand binding[120-122] or remove the transmembrane domain (amino acids 1736-1756), RAM domain (amino acids 1757-1926), ankyrin repeats (amino acids 1927-2122) and/or transactivation domain (amino acids 2123-2374) that are necessary for NOTCH1 function, such as observed here, are predicted to be inactivating[119,123-125]. Several point mutations, including D469G, A465T, C478F, R1594Q, and P1770S, have also been reported to inactivate NOTCH1[113,126-127].

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
TP53

ALTERATION
C242S

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
725G>C

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[128-131], or p53 gene therapy and immunotherapeutics such as SGT-53[132-136] and ALT-801[137]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[138]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[139]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[140]. 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[141]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[142]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[143]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[136]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[144]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[145-147]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[148]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[149-150]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[151-152]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[55-56,153-158], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[55-56,159-160]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[57-58]. 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[161]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[162].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[163]. Alterations such as seen here may disrupt TP53 function or expression[164-168].

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[169-171], including sarcomas[172-173]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[174] to 1:20,000[173]. 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[175]. 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[88-93]. 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[88-89]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[94]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[92,95-96]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Atezolizumab

Assay findings association

Blood Tumor Mutational Burden
10 Muts/Mb

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and urothelial carcinoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, hepatocellular carcinoma, and BRAF V600-positive melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,176] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The Phase 2 B-F1RST study prospectively evaluated blood tumor mutational burden (bTMB) as a biomarker of response to first-line atezolizumab in non-small cell lung cancer (NSCLC), reporting improved ORR (29% vs. 4.4%) and a trend toward improved median PFS (mPFS; 5.0 vs. 3.5 months, HR=0.80) and median OS (mOS; 23.9 vs. 13.4 months, HR=0.66) for patients with bTMB ≥16 Muts/Mb compared with bTMB <16 Muts/Mb; improved PFS and OS were seen with increasing bTMB cutoffs[177]. Retrospective analysis of the Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic NSCLC reported improved mOS (11.2 vs. 10.3 months, HR=0.87) and mPFS (5.5 vs. 4.3 months, HR=0.74) compared with chemotherapy for patients with bTMB levels ≥10 Muts/Mb (approximate equivalency ≥9 Muts/Mb as measured by this assay), with greater efficacy observed at higher bTMB cutoffs[178]. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic NSCLC reported atezolizumab significantly improved OS across bTMB levels compared with docetaxel (p=0.0001); patients with bTMB levels ≥10 Muts/Mb (approximate equivalency ≥9 Muts/Mb as measured by this assay) achieved greater clinical benefit with atezolizumab than those with bTMB <10 Muts/Mb, with greater efficacy observed at higher bTMB cutoffs[1,179] ; patients with two or more mutations in DNA damage response and repair pathway genes (DDR) had an increased bTMB (20 vs. 7 muts/Mb), and reported a superior durable clinical benefit compared with patients without DDR mutations (57% vs. 31%, p=0.003)[180]. In the Phase 3 IMpower131 study, addition of atezolizumab to first-line carboplatin and paclitaxel improved median PFS for patients with squamous NSCLC compared with chemotherapy alone (6.3 vs. 5.6 months, HR=0.71); longer PFS was observed across PD-L1 expression subgroups[181].

In the first-line setting, the Phase 3 IMpower130, IMpower150, and IMpower132 studies have shown that the addition of atezolizumab to chemotherapy-based regimens significantly improves survival for patients with non-squamous NSCLC without EGFR or ALK alterations[182-184] . In IMpower130, median PFS (7.0 vs. 5.5 months, HR=0.64) and median OS (18.6 vs. 13.9 months, HR=0.79) were significantly improved with atezolizumab plus nab-paclitaxel and carboplatin relative to chemotherapy alone; benefit was observed irrespective of PD-L1 status[183]. Similarly, IMpower150 reported improved median PFS (8.3 vs. 6.8 months, HR=0.62) and median OS (19.2 vs. 14.7 months, HR=0.78) with the addition of atezolizumab to bevacizumab, paclitaxel, and carboplatin; longer PFS was observed irrespective of PD-L1 status or KRAS mutation[182]. In IMpower132, the addition of atezolizumab to first-line carboplatin or cisplatin with pemetrexed in non-squamous NSCLC increased median PFS (7.6 vs. 5.2 months, HR=0.60) relative to chemotherapy alone[184]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic non-small cell lung cancer (NSCLC) reported improved median OS (mOS; 20.2 vs. 13.1 months, HR=0.59), median PFS (8.1 vs. 5.0 months), and ORR (38% vs. 29%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[178]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in mOS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[185], confirming previous Phase 2 trial data[186-187] . In the OAK trial, improved OS was observed for patients, regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was reported for patients with high PD-L1 tumor cell (>50%) or tumor-infiltrating immune cell (>10%) expression (HR=0.41) compared with those possessing <1% expression on either cell type (HR=0.75)[185]. Retrospective analyses of the OAK trial also identified clinical benefit for patients receiving atezolizumab and metformin compared with atezolizumab alone (ORR of 25% vs. 13%)[188], and for patients with 2 or more mutations in DNA damage response and repair pathway genes compared with those without (durable clinical benefit rate of 57% vs. 31%, p=0.003)[180]. The Phase 3 IMpower010 study of adjuvant atezolizumab treatment following adjuvant chemotherapy for patients with resected Stage II-IIIA NSCLC reported improved median disease-free survival compared with best supportive care (42.3 vs. 35.3 months, HR=0.79), with the greatest benefit observed for patients with PD-L1 tumor cell expression of ≥1% (not reached vs. 35.3 months, HR=0.66)[189]. In the randomized Phase 2 CITYSCAPE study of treatment-naive advanced NSCLC, the addition of tiragolumab to atezolizumab showed clinically meaningful improvement

in ORR (37% [25/67] vs. 21% [14/68]) and PFS (5.6 vs. 3.9 months, HR=0.58), with greater ORR (66% [19/29] vs. 24% [7/29]) and PFS (not reached vs. 4.1 months, HR=0.30) observed for patients with PD-L1 tumor proportion scores (TPS) ≥50%[190].

Cemiplimab

Assay findings association

Blood Tumor Mutational Burden
10 Muts/Mb

AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat patients with NSCLC with high PD-L1 expression (TPS ≥ 50%), cutaneous squamous cell carcinoma (CSCC), or basal cell carcinoma (BCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,176] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The Phase 3 EMPOWER-Lung 1 trial for treatment-naive advanced non-small cell lung cancer (NSCLC) reported that cemiplimab improved median PFS (mPFS, 8.2 vs. 5.7 months, hazard ratio [HR]=0.54), median OS (mOS, not reached vs. 14.2 months, HR=0.57), and ORR (39% vs. 20%) compared with chemotherapy in patients with high PD-L1 expression (TPS ≥ 50%); improved mPFS (6.2 vs. 5.6 months, HR=0.59), mOS (22.1 vs. 14.3 months, HR=0.68), and ORR (37% vs. 21%) were also reported for cemiplimab over chemotherapy in the intention-to-treat population[191]. In a Phase 2 trial of cemiplimab-containing regimens as second-line therapy for NSCLC, cemiplimab combined with ipilimumab elicited a numerically higher ORR (46% [5/11]) compared with high-dose (11% [1/9]) and standard-dose cemiplimab monotherapy (0% [0/8])[192].

Dostarlimab

Assay findings association

Blood Tumor Mutational Burden
10 Muts/Mb

AREAS OF THERAPEUTIC USE

Dostarlimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor response. It is FDA approved to treat patients with mismatch repair deficient recurrent or advanced endometrial cancer or solid tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,176] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In the Phase 1 GARNET trial of dostarlimab, patients with non-small cell lung cancer (NSCLC) experienced an immune-related ORR (irORR) of 27% with 2 CRs[193]. Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[194-196] . In the Phase 1 GARNET trial, single-agent dostarlimab elicited an ORR of 39% (41/106) and an immune-related ORR of 46% (50/110) for patients with non-endometrial dMMR solid tumors[194,197] .

Durvalumab

Assay findings association

Blood Tumor Mutational Burden
10 Muts/Mb

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,176] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The MYSTIC trial for patients with treatment-naïve, EGFR/ALK-negative metastatic NSCLC reported that a bTMB score ≥20 Muts/Mb (approximately 10 Muts/Mb as measured by this assay) associated with improved survival following either a combination treatment of durvalumab with the CTLA-4 inhibitor tremelimumab, regardless of tumor PD-L1 expression, or following durvalumab monotherapy for patients with tumor cell PD-L1 expression <1%[176]. In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable non-small cell lung cancer (NSCLC) who did not have progression on chemoradiotherapy, durvalumab monotherapy improved PFS versus placebo across PD-L1 expression subgroups; median PFS (mPFS) was 23.9 versus 5.6 months (HR=0.49) for patients with PD-L1 expression ≥1% and 10.7 versus 5.6 months (HR=0.79) for patients with PD-L1 expression <1%. Median OS (mOS) benefit was observed for patients with PD-L1 expression ≥1% (57.4 vs. 29.6 months, HR=0.60), but not for those with PD-L1 expression <1% (33.9 vs. 43.0 months, HR=1.05)[198-199] . In the Phase 3 ARCTIC study for patients with metastatic NSCLC who had progressed on 2 or fewer prior therapies, single-agent durvalumab improved OS (11.7 vs. 6.8 months, HR=0.63) and PFS (3.8 vs. 2.2 months, HR=0.71) versus the investigator's choice of standard of care (SOC) for patients in cohort A (PD-L1 ≥25%)[200]. However, durvalumab plus tremelimumab did not significantly improve OS (11.5 vs. 8.7 months, HR=0.80) or PFS (3.5 vs. 3.5 months, HR=0.77) compared with SOC for patients in cohort B (PD-L1 <25%)[200]. In the Phase 3 MYSTIC trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC and PD-L1 expression ≥25%, neither durvalumab monotherapy nor durvalumab plus tremelimumab improved OS versus chemotherapy (HR=0.76 vs. HR=0.85); however, patients with blood tumor mutational burden (bTMB) ≥20 Muts/Mb showed improved OS for durvalumab plus tremelimumab versus chemotherapy (21.9 vs. 10.0 months, HR=0.49)[201]. In the Phase 3 POSEIDON trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC, the addition of durvalumab and tremelimumab to chemotherapy improved mOS (14.0 vs. 11.7 months, HR=0.77) and mPFS (6.2 vs 4.8 months, HR=0.72) versus chemotherapy[202]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[203-204] and OS[203] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90%) had an ORR of 31% (21/68) compared with ORRs of 16% (24/146) for patients with ≥25% and 7.5% (7/93) for patients with <25% PD-L1 positivity[204]. Re-treatment with durvalumab for patients with PD-L1-positive (≥25%) EGFR-negative or ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or SD for 25% (10/40) of patients[205].

Nivolumab

Assay findings association

Blood Tumor Mutational Burden
10 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved as monotherapy in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma or squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). It is also approved in combination with cabozantinib to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,176] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

For patients with platinum-refractory non-squamous non-small cell lung cancer (NSCLC), nivolumab improved median OS (mOS; 12.2 vs. 9.4 months) and ORR (19% vs. 12%) compared with docetaxel in the Phase 3 CheckMate 057 study; PD-L1 expression was associated with OS benefit from nivolumab in this study (HR=0.40-0.59)[206]. In advanced squamous NSCLC, second-line nivolumab resulted in longer mOS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel in the Phase 3 CheckMate 017 study; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[207-208] . Pooled analysis of CheckMate 057 and CheckMate 017 showed improved long-term OS and PFS benefit for nivolumab over docetaxel, with 5-year OS rates of 13% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[209]. In the CheckMate 227 study, the combination of nivolumab and platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[210], despite Phase 1 results in the same setting suggesting improved ORR and OS[211]. In the Phase 3 CheckMate 816 study, the combination of nivolumab and platinum-based doublet chemotherapy did show benefit as a neoadjuvant treatment for patients with resectable NSCLC, reporting a pathological CR (pCR) rate of 24% versus 2.2% for chemotherapy alone, and the benefit was consistent across subgroups stratified by PD-L1 expression, stage of disease, or tumor mutational burden (TMB)[212]. A Phase 1 study of nivolumab combined with the immunostimulatory therapy bempegaldesleukin for immunotherapy-naive patients with NSCLC reported an ORR of 60% (3/5; 2 CRs) and mPFS of 18.0 months[213].

Pembrolizumab

Assay findings association

Blood Tumor Mutational Burden
10 Muts/Mb

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved for patients with tumor mutational burden (TMB)-high (≥10 Muts/Mb), microsatellite instability-high (MSI-H), or mismatch repair-deficient (dMMR) solid tumors; as monotherapy for PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), cervical cancer, or gastric, esophageal, or gastroesophageal junction (GEJ) cancer; and in combination with chemotherapy for PD-L1-positive triple-negative breast cancer (TNBC) or cervical cancer. It is also approved in various treatment settings as monotherapy for patients with melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, classical Hodgkin lymphoma, or primary mediastinal large B-cell lymphoma, and in combination with chemotherapy or targeted therapy for NSCLC, HNSCC, esophageal or GEJ cancer, renal cell carcinoma, TNBC, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information. A voluntary withdrawal of the accelerated approval of pembrolizumab for the treatment of patients with recurrent advanced PD-L1-positive gastric or GEJ adenocarcinoma with disease progression on or after two or more prior lines of therapy has been initiated by the manufacturer.

GENE ASSOCIATION

On the basis of clinical data[1-3,176] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

A pilot study for first-line pembrolizumab alone or in combination with chemotherapy, for patients with newly diagnosed metastatic NSCLC, reported significantly improved median PFS in patients with bTMB levels ≥16 Muts/Mb (approximately 8 Muts/Mb as measured by this assay) compared with those with bTMB <16 Muts/Mb (14.1 vs. 4.7 months, HR=0.30); median OS was not reached in the bTMB ≥16 Muts/Mb cohort, compared with 8.8 months for those with bTMB <16 (HR=0.48)[3]. The superiority of pembrolizumab over platinum chemotherapy as first-line treatment for patients with PD-L1-positive non-small cell lung cancer (NSCLC) lacking EGFR or ALK alterations was demonstrated in the Phase 3 KEYNOTE-042 and -024 studies, which reported improved median OS (mOS) for PD-L1 tumor proportion scores (TPS) ≥1% (16.7 vs. 12.1 months, HR=0.81)[214] and ≥50% (26.3 vs. 13.4 months, HR=0.62-0.69)[215], with estimated 5-year OS rates of 32% versus 16% in the KEYNOTE-024 study[215]. In the Phase 1b KEYNOTE-100 study of pembrolizumab, mOS was numerically higher for patients with NSCLC and PD-L1 TPS ≥50% relative to those with lower levels of PD-L1 expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[216]. A retrospective study showed that among patients with NSCLC and high PD-L1 expression treated with first-line pembrolizumab, mOS was improved for patients with TPS of 90-100% relative to those with TPS of 50-89% (not reached vs. 15.9 months, HR=0.39)[217]. Phase 3 studies showed that the addition of pembrolizumab to chemotherapy is superior to chemotherapy alone in the first-line setting for patients with either non-squamous (KEYNOTE-189)[218] or squamous (KEYNOTE-407)[219-220] NSCLC, regardless of PD-L1 or tumor mutational burden (TMB) status[221]. An exploratory analysis of KEYNOTE-189 demonstrated the superiority of the pembrolizumab combination therapy, regardless of blood TMB (bTMB) status[222]. For the first-line treatment of patients with NSCLC and high PD-L1 expression (TPS ≥50%), a meta-analysis of KEYNOTE-024 and -189 reported the combination of pembrolizumab and chemotherapy to be non-superior to pembrolizumab alone in terms of survival benefit; however, the combination did increase ORR (+22%, p=0.011)[223]. In the Phase 2/3 KEYNOTE-010 study, pembrolizumab extended mOS relative to docetaxel (10.4-12.7 vs. 8.2 months) for patients with previously treated PD-L1-positive NSCLC[224]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single agent and in combination with chemotherapy, to treat patients with NSCLC and brain metastases[225-227] . Clinical activity has also been achieved with pembrolizumab in combination with the AXL inhibitor bemcentinib[228], the anti-CTLA-4 antibody ipilimumab[229], the anti-TIGIT antibody vibostolimab[230], the HDAC inhibitor vorinostat[231], the multikinase inhibitor lenvatinib[232], and the PARP inhibitor niraparib[233].

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Avelumab

Assay findings association

Blood Tumor Mutational Burden
10 Muts/Mb

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with Merkel cell carcinoma, or for urothelial carcinoma in various treatment settings. The combination of avelumab and axitinib is FDA approved for patients with renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,176] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In the Phase 3 JAVELIN Lung 200 study for patients with advanced non-small cell lung cancer (NSCLC) previously treated with platinum therapy, avelumab did not improve median OS (mOS) when compared with docetaxel (11.4 vs. 10.6 months; HR=0.87) for patients with PD-L1 expression in ≥1% of tumor cells; a prespecified exploratory analysis at higher PD-L1 expression cutoffs showed improved mOS for PD-L1 ≥50% (13.6 vs. 9.2 months; HR=0.67) and ≥80% (17.1 vs. 9.3 months; HR=0.59)[234], and improved 2-year OS rates of 30% versus 21% (≥1% PD-L1), 36% versus 18% (≥50% PD-L1), and 40% versus 20% (≥80% PD-L1)[235]. A post-hoc analysis of this study suggested that a relatively high proportion of patients in the docetaxel arm received subsequent immune checkpoint inhibitor treatment, which may have confounded the outcomes of this study[236]. A Phase 1 study evaluating single-agent avelumab to treat patients with advanced NSCLC reported an ORR of 20%, median PFS (mPFS) of 4.0 months, and mOS of 14.1 months in the first-line setting[237]. A Phase 2 study of avelumab with axitinib to treat advanced NSCLC reported an ORR of 32% (13/41) and mPFS of 5.5 months; tumor reduction was observed for PD-L1-negative and -positive (≥1% PD-L1) samples[238]. A Phase 1b/2 study of avelumab combined with the anti-semaphorin 4D antibody pepinemab to treat advanced NSCLC reported an ORR of 24% (5/21) and DCR of 81% for immunotherapy-naive patients, and ORR of 6.9% (2/29) and DCR of 59% for patients who had disease progression on prior immunotherapy treatment[239]. A study of neoadjuvant avelumab plus chemotherapy to treat early-stage resectable NSCLC reported an ORR of 27% (4/15), which was not considered an enhancement over chemotherapy alone[240].

Selumetinib

Assay findings association

NF1
splice site 6705-2A>C, Y863fs*15

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[38-41,241-245] , glioma[41-45,246] , and non-small cell lung cancer[46], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

In the Phase 2 umbrella trial National Lung Matrix Trial, selumetinib plus docetaxel yielded an ORR of 29% (4/14) for patients with lung adenocarcinoma harboring NF1 loss[46]. In a Phase 2 study of selumetinib monotherapy to treat patients with lung cancer who were selected for mutation in KRAS, HRAS, NRAS, or BRAF, a mPFS of 2.3 months and mOS of 6.5 months was observed[247]. In a Phase 2 study of patients with NSCLC who had failed on at least 2 prior chemotherapeutic regimes, selumetinib as a monotherapy did not improve survival as compared to pemetrexed (67 vs 90 days, HR= 1.08); however, 2 PRs were reported[248]. A Phase 2 study of selumetinib combined with docetaxel for patients with advanced or metastatic KRAS wild-type NSCLC who were previously treated did not report improved survival benefit compared to docetaxel alone[249]. A Phase 2 study of selumetinib combined with pemetrexed and platinum based chemotherapy for treatment of patients with advanced non-squamous NSCLC showed improved ORR (35% with intermittent dosing and 62% for continuous dosing) compared to chemotherapy alone (24%) but did not report a statistically significant improvement in mPFS[250]. The combination of selumetinib with platinum doublet chemotherapy has been studied in a Phase 1 trial for patients with advanced NSCLC in the first line setting and has reported 4/21 PRs in the selumetinib + pemetrexed/carboplatin cohort and 2/15 PRs in the pemetrexed/cisplatin cohort; selumetinib in combination with gemcitabine regimens was not tolerated[251]. A Phase 1b study of selumetinib in combination with osimertinib for patients with EGFR-mutated lung cancer who had progressed on previous TKI treatment reported an ORR of 41.7% (15/36)[252].

Trametinib

Assay findings association

NF1
splice site 6705-2A>C, Y863fs*15

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[38-41,241-245] , glioma[41-45,246] , and non-small cell lung cancer[46], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

For patients with previously treated BRAF V600E-mutated metastatic NSCLC, trametinib in combination with the BRAF inhibitor dabrafenib achieved an ORR of 63% (36/57), including 2 CRs and 34 PRs, a DCR (CRs, PRs, and SD) of 79% (45/57), and a median PFS of 9.7 months[253]. Dabrafenib plus trametinib demonstrated similar activity as first-line therapy for BRAF V600E-mutated metastatic NSCLC, with an ORR of 64% (23/36) and a median PFS of 10.9 months[254]. Phase 1 and 2 monotherapy trials of MEK inhibitors such as trametinib and RO4987655 have shown low response rates in patients with NSCLC, irrespective of KRAS mutation status, and no improvement in PFS compared to docetaxel[255-257] . However, Phase 1 and 2 trials of MEK inhibitors in combination with docetaxel or pemetrexed in NSCLC have shown improved clinical activity and patient survival compared to chemotherapeutics alone, although no association was observed between response and KRAS mutation status[258-260] . In contrast, although 3 objective responses were observed in patients with NSCLC treated with the MEK inhibitor selumetinib in combination with erlotinib in a Phase 2 trial, there was no significant increase in either PFS or OS relative to patients treated with selumetinib alone; further, the combination increased toxicity relative to monotherapy[261]. Preclinical and early clinical studies have shown synergistic antitumorigenic effects when the combination of MEK and PI3K inhibitors was used to treat KRAS-driven NSCLC[262-264] . A Phase 1b combination trial of trametinib and the pan-PI3K inhibitor BKM120 reported a DCR of 59% in patients with NSCLC, including 1 confirmed PR in 17 patients; although the reported adverse effects were prevalent and often severe, the study recommended a Phase 2 dose[265]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[53], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[54].

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

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

ORDERED TEST # ORD-1269154-01

CLINICAL TRIALS

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.

BIOMARKER

Blood Tumor Mutational Burden

RESULT

10 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

NCT03800134

PHASE 3

A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer

TARGETS
PD-L1

LOCATIONS: San Isidro (Peru), Lima (Peru), Bellavista (Peru), San Salvador de Jujuy (Argentina), Viña del Mar (Chile), Santiago (Chile), San José (Costa Rica), Rosario (Argentina), Pergamino (Argentina), Temuco (Chile)

NCT03735121

PHASE 3

A Study to Investigate the Pharmacokinetics, Efficacy, and Safety of Atezolizumab Subcutaneous in Patients With Stage IV Non-Small Cell Lung Cancer

TARGETS
PD-L1, VEGFA

LOCATIONS: Arequipa (Peru), Lima (Peru), Salta (Argentina), La Rioja (Argentina), Vina Del Mar (Chile), Recoleta (Chile), San José (Costa Rica), Temuco (Chile), Buenos Aires (Argentina), Guatemala (Guatemala)

NCT04294810

PHASE 3

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT

LOCATIONS: San Isidro (Peru), Lima (Peru), Arequipa (Peru), Ijui (Brazil), Barretos (Brazil), Porto Alegre (Brazil), Cdmx (Mexico), Mexico (Mexico), Querétaro (Mexico), Florida

NCT04385368

PHASE 3

Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Lima (Peru), Bellavista (Peru), Ciudad Autonoma De Buenos Aire (Argentina), Texas, Alabama, Georgia, South Carolina, North Carolina, Tennessee, Kentucky

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

ORDERED TEST # ORD-1269154-01

CLINICAL TRIALS

NCT04380636

PHASE 3

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

TARGETS
PD-L1, PARP, PD-1

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

NCT04521621

PHASE 1/2

A Study of V937 in Combination With Pembrolizumab (MK-3475) in Participants With Advanced/ Metastatic Solid Tumors (V937-013)

TARGETS
PD-1

LOCATIONS: Lima (Peru), Taichung (Taiwan), New Jersey, Toronto (Canada), Montreal (Canada), Oregon, Madrid (Spain), Barcelona (Spain), Villejuif (France), Marseille (France)

NCT03976375

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Lenvatinib (E7080/MK-7902) vs. Docetaxel in Participants With Metastatic Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease (PD) After Platinum Doublet Chemotherapy and Immunotherapy (MK-7902-008/E7080-G000-316/LEAP-008)

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

LOCATIONS: Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Barranquilla (Colombia), Rosario (Argentina), Caba (Argentina), Buenos Aires (Argentina), Ponce (Puerto Rico)

NCT03703297

PHASE 3

Study of Durvalumab + Tremelimumab, Durvalumab, and Placebo in Limited Stage Small-Cell Lung Cancer in Patients Who Have Not Progressed Following Concurrent Chemoradiation Therapy

TARGETS
PD-L1, CTLA-4

LOCATIONS: San Salvador de Jujuy (Argentina), Córdoba (Argentina), Rosario (Argentina), Mar del Plata (Argentina), Caba (Argentina), La Plata (Argentina), Florida, Georgia

NCT04738487

PHASE 3

Vibostolimab (MK-7684) With Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab (MK-3475) Monotherapy for Programmed Cell Death 1 Ligand 1 (PD-L1) Positive Metastatic Non-Small Cell Lung Cancer (MK-7684A-003)

TARGETS
TIGIT, PD-1

LOCATIONS: La Serena (Chile), Guatemala (Guatemala), Guatemala City (Guatemala), Florida, Hsinchu (Taiwan), Missouri, Illinois, Kharkiv (Ukraine), Kryvyi Rih (Ukraine)

NCT03425643

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage IIB or IIIA Non-small Cell Lung Cancer (MK-3475-671/KEYNOTE-671)

TARGETS
PD-1

LOCATIONS: San Juan (Argentina), Cordoba (Argentina), Rosario (Argentina), Ijui (Brazil), Berazategui (Argentina), Brasilia (Brazil), Barretos (Brazil), Porto Alegre (Brazil), Florianopolis (Brazil), Sao Paulo (Brazil)

GENE
NF1

ALTERATION
splice site 6705-2A>C, Y863fs*15

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT03600701

PHASE 2

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

TARGETS
PD-L1, MEK

LOCATIONS: Florida, Alabama, North Carolina, Virginia, District of Columbia, Oklahoma, Ohio, Michigan, New Hampshire

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Florida, Georgia, Texas, North Carolina, Tennessee, Virginia, Oklahoma, Maryland, Pennsylvania, Ohio

NCT01737502

PHASE 1/2

Sirolimus and Auranofin in Treating Patients With Advanced or Recurrent Non-Small Cell Lung Cancer or Small Cell Lung Cancer

TARGETS
mTOR

LOCATIONS: Florida

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

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

NCT03334617

PHASE 2

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

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

LOCATIONS: Texas, Tennessee, Virginia, District of Columbia, Maryland, Missouri, Pennsylvania, New York, Massachusetts

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

NCT03337698

PHASE 1/2

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

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

LOCATIONS: Tennessee, Ohio, Nevada, Malaga (Spain), Madrid (Spain), Valencia (Spain), Pamplona (Spain), Saint Herblain (France), Barcelona (Spain), Toulouse (France)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, ROS1, AXL, TRKA, MET, TRKC, MEK, AKTs, EGFR, PD-L1, KIT, DDR2, VEGFRs, PDGFRA, FLT3, RET, TRKB

LOCATIONS: Exeter (United Kingdom), Belfast (United Kingdom), Cardiff (United Kingdom), Bristol (United Kingdom), Wirral (United Kingdom), Southampton (United Kingdom), Glasgow (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

NCT04185831

PHASE 2

A MolEcularly Guided Anti-Cancer Drug Off-Label Trial

TARGETS
PD-L1, MEK, mTOR

LOCATIONS: Gothenburg (Sweden), Uppsala (Sweden)

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.

AKT1
R328H

CARD11
E343D

DNMT3A
P750T

DOT1L
A935T

FGFR2
Q43K and R152K

FLT3
D469E

GNAS
A210P

MDM4
P369R

PTPN11
H426R

RAC1
V152A

SMO
R772L

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

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

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

ORDERED TEST # ORD-1269154-01

APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

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

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF THERAPIES AND CLINICAL TRIALS

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

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

LIMITATIONS

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

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

REPORT HIGHLIGHTS

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

SELECT ABBREVIATIONS

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

MR Suite Version 5.2.0

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
4. Li et al., 2020; ASCO Abstract 6511
5. Nie W, et al. J Natl Compr Canc Netw (2020) pmid: 32380463
6. Ma Y, et al. Front Oncol (2021) pmid: 34055609
7. Xiao D, et al. Oncotarget (2016) pmid: 27009843
8. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
9. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
10. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
11. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
12. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
13. Rizvi NA, et al. Science (2015) pmid: 25765070
14. Johnson BE, et al. Science (2014) pmid: 24336570
15. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
16. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
17. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
18. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
19. Nature (2012) pmid: 22810696
20. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
21. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
22. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
23. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
24. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
25. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
26. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
27. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
28. Lapin M, et al. J Transl Med (2018) pmid: 30400802
29. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
30. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
31. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
32. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
33. Fan G, et al. PLoS ONE (2017) pmid: 28187169
34. Vu et al., 2020; DOI: 10.1200/PO.19.00204
35. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
36. Zhang EW, et al. Cancer (2020) pmid: 32757294
37. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
38. Dombi E, et al. N. Engl. J. Med. (2016) pmid: 28029918
39. Schalkwijk S, et al. Cancer Chemother Pharmacol (2021) pmid: 33903938
40. Toledano H, et al. Childs Nerv Syst (2021) pmid: 33751171
41. Ronsley R, et al. Cancer Med (2021) pmid: 33939292
42. Fangusaro J, et al. Lancet Oncol. (2019) pmid: 31151904
43. Manoharan N, et al. J Neurooncol (2020) pmid: 32780261
44. Kondyli M, et al. J Neurooncol (2018) pmid: 30097824
45. Awada G, et al. Case Rep Oncol () pmid: 33082744
46. Middleton G, et al. Nature (2020) pmid: 32669708
47. Lim SM, et al. Oncotarget (2016) pmid: 26859683
48. Weiss B, et al. Neuro-oncology (2015) pmid: 25314964
49. Janku F, et al. Oncotarget (2014) pmid: 24931142
50. Johannessen CM, et al. Curr. Biol. (2008) pmid: 18164202
51. Johannessen CM, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15937108
52. Malone CF, et al. Cancer Discov (2014) pmid: 24913553
53. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
54. Patterson et al., 2018; AACR Abstract 3891
55. Nature (2014) pmid: 25079552
56. Nature (2012) pmid: 22960745
57. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
58. Gao J, et al. Sci Signal (2013) pmid: 23550210
59. de Bruin EC, et al. Cancer Discov (2014) pmid: 24535670
60. Hattori S, et al. Biochem. Biophys. Res. Commun. (1991) pmid: 1904223
61. Morcos P, et al. Mol. Cell. Biol. (1996) pmid: 8628317
62. Ballester R, et al. Cell (1990) pmid: 2121371
63. Xu GF, et al. Cell (1990) pmid: 2116237
64. Martin GA, et al. Cell (1990) pmid: 2121370
65. Thomas L, et al. Hum. Mutat. (2012) pmid: 22807134
66. Skuse GR, et al. Hum. Mol. Genet. (1997) pmid: 9300663
67. Messiaen LM, et al. Genet. Med. () pmid: 11258625
68. Ars E, et al. Hum. Mol. Genet. (2000) pmid: 10607834
69. Messiaen LM, et al. J. Med. Genet. (2005) pmid: 15863657
70. Poullet P, et al. Mol. Cell. Biol. (1994) pmid: 8264648
71. Jett K, et al. Genet. Med. (2010) pmid: 20027112
72. Patil S, et al. Oncologist (2012) pmid: 22240541
73. Evans DG, et al. Clin Sarcoma Res (2012) pmid: 23036231
74. Upadhyaya M, et al. J. Med. Genet. (1995) pmid: 8544190
75. Williams VC, et al. Pediatrics (2009) pmid: 19117870
76. Trowbridge JJ, et al. Nat. Genet. (2011) pmid: 22200773
77. Prog Mol Biol Transl Sci (2011) pmid: 21507354
78. Yang J, et al. Mol Med Rep () pmid: 21887466
79. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
80. Daskalos A, et al. Cancer (2011) pmid: 21351083
81. Fabbri M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17890317
82. Gao Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22011581
83. Kim MS, et al. APMIS (2013) pmid: 23031157
84. Chen ZX, et al. J. Cell. Biochem. (2005) pmid: 15861382
85. Guo X, et al. Nature (2015) pmid: 25383530
86. Sandoval JE, et al. J. Biol. Chem. (2019) pmid: 30705090
87. Zhang ZM, et al. Nature (2018) pmid: 29414941
88. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
89. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
90. Xie M, et al. Nat. Med. (2014) pmid: 25326804
91. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
92. Severson EA, et al. Blood (2018) pmid: 29678827
93. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
94. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
95. Chabon JJ, et al. Nature (2020) pmid: 32269342
96. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
97. Debeb BG, et al. Breast Cancer Res. Treat. (2012) pmid: 22547109
98. Fouladi M, et al. J. Clin. Oncol. (2011) pmid: 21825264
99. Groth C, et al. Semin. Cell Dev. Biol. (2012) pmid: 22309842
100. Kamstrup MR, et al. Blood (2010) pmid: 20538790
101. Kridel R, et al. Blood (2012) pmid: 22210878
102. Krop I, et al. J. Clin. Oncol. (2012) pmid: 22547604
103. Rosati E, et al. Int. J. Cancer (2013) pmid: 23001755
104. Samon JB, et al. Mol. Cancer Ther. (2012) pmid: 22504949
105. Ferrarotto et al., 2020; ESMO Abstract 919MO
106. Knoechel B, et al. Cold Spring Harb Mol Case Stud (2015) pmid: 27148573
107. Dreyling M, et al. Ann. Oncol. (2017) pmid: 28633365
108. Palomero T, et al. Nat. Med. (2007) pmid: 17873882
109. Liu S, et al. Urol. Oncol. (2013) pmid: 21993533
110. Zhang K, et al. Clin. Cancer Res. (2020) pmid: 32241817
111. Westhoff B, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 20007775
112. Li Y, et al. Biologics (2010) pmid: 20631820
113. Wang NJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22006338
114. Hassan KA, et al. Clin. Cancer Res. (2013) pmid: 23444212
115. Ye YZ, et al. Med. Oncol. (2013) pmid: 23645556
116. Liu YP, et al. Cancer Res. (2013) pmid: 23135908
117. Klinakis A, et al. Nature (2011) pmid: 21562564
118. Penton AL, et al. Semin. Cell Dev. Biol. (2012) pmid: 22306179
119. Kopan R, et al. Cell (2009) pmid: 19379690
120. Andrawes MB, et al. J. Biol. Chem. (2013) pmid: 23839946
121. Rebay I, et al. Cell (1991) pmid: 1657403
122. Ge C, et al. BMC Dev. Biol. (2008) pmid: 18445292
123. Aster JC, et al. Mol. Cell. Biol. (2000) pmid: 11003647
124. Weng AP, et al. Science (2004) pmid: 15472075
125. Deregowski V, et al. J. Bone Miner. Res. (2006) pmid: 16869730
126. Uchibori M, et al. Oncol. Rep. (2017) pmid: 28791383
127. Liu J, et al. Proc Natl Acad Sci U S A (2013) pmid: 24277854
128. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
129. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
130. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
131. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
132. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
133. Xu L, et al. Mol. Med. (2001) pmid: 11713371
134. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
135. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
136. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
137. Hajdenberg et al., 2012; ASCO Abstract e15010
138. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
139. Moore et al., 2019; ASCO Abstract 5513
140. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
141. Oza et al., 2015; ASCO Abstract 5506
142. Lee J, et al. Cancer Discov (2019) pmid: 31315834
143. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
144. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
145. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
146. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
147. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
148. Gourley et al., 2016; ASCO Abstract 5571
149. Kwok M, et al. Blood (2016) pmid: 26563132
150. Boudny M, et al. Haematologica (2019) pmid: 30975914
151. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
152. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
153. Mogi A, et al. J. Biomed. Biotechnol. (2011) pmid:

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

21331359
154. Tekpli X, et al. Int. J. Cancer (2013) pmid: 23011884
155. Vignot S, et al. J. Clin. Oncol. (2013) pmid: 23630207
156. Maeng CH, et al. Anticancer Res. (2013) pmid: 24222160
157. Cortot AB, et al. Clin Lung Cancer (2014) pmid: 24169260
158. Itakura M, et al. Br. J. Cancer (2013) pmid: 23922113
159. Imielinski M, et al. Cell (2012) pmid: 22980975
160. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
161. Dong ZY, et al. Clin. Cancer Res. (2017) pmid: 28039262
162. Seo JS, et al. Genome Res. (2012) pmid: 22975805
163. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
164. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
165. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
166. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
167. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
168. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
169. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
170. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
171. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
172. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
173. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
174. Lalloo F, et al. Lancet (2003) pmid: 12672316
175. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
176. Rizvi et al., 2019; ASCO Abstract 9016
177. Socinski et al., 2019; ESMO Abstract LBA83
178. Herbst RS, et al. N Engl J Med (2020) pmid: 32997907
179. Chen YT, et al. Front Oncol (2019) pmid: 31921683
180. Nie et al., 2020; WCLC Abstract OA07.03
181. Jotte R, et al. J Thorac Oncol (2020) pmid: 32302702
182. Socinski MA, et al. N. Engl. J. Med. (2018) pmid: 29863955
183. West H, et al. Lancet Oncol. (2019) pmid: 31122901
184. Barlesi et al., 2018; ESMO Abstract LBA54
185. Rittmeyer A, et al. Lancet (2017) pmid: 27979383
186. Smith et al., 2016; ASCO Abstract 9028
187. Fehrenbacher L, et al. Lancet (2016) pmid: 26970723
188. Pietras et al., 2018; WCLC Abstract P1.04-3
189. Felip E, et al. Lancet (2021) pmid: 34555333
190. Rodriguez-Abreu et al., 2020; ASCO Abstract 9503
191. Sezer A, et al. Lancet (2021) pmid: 33581821
192. Shim et al., 2020; ESMO Abstract 1269P
193. Subramanian et al., 2020; ESMO Abstract 1399P
194. Andre et al., 2021; ASCO GI Abstract 9
195. Oaknin A, et al. JAMA Oncol (2020) pmid: 33001143
196. Berton et al., 2021; ASCO Abstract 2564
197. Andre et al., 2021; ESMO GI Abstract SO-9
198. Paz-Ares L, et al. Ann. Oncol. (2020) pmid: 32209338
199. Faivre-Finn C, et al. J Thorac Oncol (2021) pmid: 33476803
200. Planchard D, et al. Ann. Oncol. (2020) pmid: 32201234
201. Rizvi NA, et al. JAMA Oncol (2020) pmid: 32271377
202. Johnson et al., 2021; WCLC Abstract PL02.01
203. Antonia SJ, et al. J Thorac Oncol (2019) pmid: 31228626
204. Garassino MC, et al. Lancet Oncol. (2018) pmid: 29545095
205. Garassino et al., 2018; WCLC Abstract P1.01-21
206. Borghaei H, et al. N. Engl. J. Med. (2015) pmid: 26412456
207. Brahmer J, et al. N. Engl. J. Med. (2015) pmid: 26028407
208. Rizvi NA, et al. Lancet Oncol. (2015) pmid: 25704439
209. Lind et al., 2020; BTOG Abstract 113
210. Paz-Ares et al., 2019; ESMO Immuno-Oncology Congress Abstract LBA3
211. Rizvi NA, et al. J. Clin. Oncol. (2016) pmid: 27354481
212. Forde et al., 2021; AACR Abstract CT003
213. Diab A, et al. Cancer Discov (2020) pmid: 32439653
214. Mok TSK, et al. Lancet (2019) pmid: 30955977
215. Brahmer et al., 2020; ESMO LBA51
216. Garon EB, et al. J. Clin. Oncol. (2019) pmid: 31154919
217. Aguilar EJ, et al. Ann. Oncol. (2019) pmid: 31435660
218. Gadgeel S, et al. J. Clin. Oncol. (2020) pmid: 32150489
219. Paz-Ares L, et al. N. Engl. J. Med. (2018) pmid: 30280635
220. Paz-Ares L, et al. J Thorac Oncol (2020) pmid: 32599071
221. Paz-Ares et al., 2019; ESMO Abstract LBA80
222. Garassino et al., 2020; ASCO Abstract 9521
223. Doherty et al., 2018; WCLC Abstract P1.01-16
224. Herbst RS, et al. Lancet (2016) pmid: 26712084
225. Powell et al., 2019; ESMO Abstract 1483PD
226. Mansfield et al., 2019; ESMO Abstract 1482O
227. Goldberg SB, et al. Lancet Oncol. (2016) pmid: 27267608
228. Spicer et al., 2020; SITC Abstract 362
229. Gubens MA, et al. Lung Cancer (2019) pmid: 30885353
230. Niu et al., 2020; ESMO Abstract 1410P
231. Gray JE, et al. Clin. Cancer Res. (2019) pmid: 31409616
232. Brose et al., 2019; DOI: 10.1200/JCO.2019.37.8_suppl.16
233. Ramalingam SS, et al. Cancer (2021) pmid: 34478166
234. Barlesi F, et al. Lancet Oncol (2018) pmid: 30262187
235. Park K, et al. J Thorac Oncol (2021) pmid: 33845211
236. Park K, et al. Lung Cancer (2021) pmid: 33636453
237. Verschraegen CF, et al. J Immunother Cancer (2020) pmid: 32907924
238. Galffy et al., 2020; SITC Abstract 281
239. Shafique M, et al. Clin Cancer Res (2021) pmid: 33820783
240. Tfayli A, et al. Cancer Med (2020) pmid: 32991781
241. Glassberg et al., 2020; ASPHO Abstract 2015
242. Coyne et al., 2020; ASCO Abstract 3612
243. McCowage et al., 2018; ASCO Abstract 10504
244. Mueller et al., 2020; SNO Abstract NFB-17
245. Waldner et al., 2020; DOI: 10.1055/s-0040-1715638
246. Romo et al., 2019; SNO Abstract RARE-54
247. Lopez-Chavez A, et al. J. Clin. Oncol. (2015) pmid: 25667274
248. Hainsworth JD, et al. J Thorac Oncol (2010) pmid: 20802351
249. Soria JC, et al. Ann. Oncol. (2017) pmid: 29045535
250. Melosky B, et al. Lung Cancer (2019) pmid: 31200828
251. Greystoke A, et al. Br. J. Cancer (2017) pmid: 28950288
252. Oxnard GR, et al. Ann. Oncol. (2020) pmid: 32139298
253. Planchard D, et al. Lancet Oncol. (2016) pmid: 27283860
254. Planchard D, et al. Lancet Oncol. (2017) pmid: 28919011
255. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
256. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
257. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
258. Kelly et al., 2013; ASCO Abstract 8027
259. Gandara et al., 2013; ASCO Abstract 8028
260. Jänne PA, et al. Lancet Oncol. (2013) pmid: 23200175
261. Carter CA, et al. Ann. Oncol. (2016) pmid: 26802155
262. Banerji et al., 2014; ASCO Abstract e13559
263. Castellano E, et al. Cancer Cell (2013) pmid: 24229709
264. Ku BM, et al. Invest New Drugs (2015) pmid: 25342139
265. Bedard PL, et al. Clin. Cancer Res. (2015) pmid: 25500057

Electronically signed by Donna Ferguson, M.D. | 03 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531