FOUNDATIONONE® LIQUID CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma

COUNTRY CODE
CZ

REPORT DATE

ORDERED TEST #

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

PATIENT

DISEASE Lung adenocarcinoma
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Genomic Signatures

Blood Tumor Mutational Burden - 6 Muts/Mb
Microsatellite status - Cannot Be Determined
Tumor Fraction - Cannot Be Determined

Gene Alterations

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

NF1 S892fs*10
ROS1 CD74-ROS1 fusion
TP53 I332fs*24

9 Therapies Approved in the EU
0 Therapies with Lack of Response
18 Clinical Trials

GENOMIC SIGNATURES

Blood Tumor Mutational Burden - 6 Muts/Mb

Microsatellite status - Cannot Be Determined

Tumor Fraction - Cannot Be Determined

GENE ALTERATIONS		VAF %
ROS1 -	CD74-ROS1 fusion	0.38%
10 Trials see p. 14		
NF1 -	S892fs*10	0.99%
10 Trials see p. 12		

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Genomic Signatures section

Unable to determine Microsatellite status due to insufficient evidence of genomic instability.

Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.

THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)		THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
Ceritinib	2A	Cabozantinib
Crizotinib	2A	
Entrectinib▼	2A	
Lorlatinib	2A	
Brigatinib		
Trametinib		Binimetinib
		Cobimetinib

☐ *NCCN category*

▼ Tento léčivý přípravek podléhá dalšímu sledování. To umožní rychlé získání nových informací o bezpečnosti. Žádáme zdravotnické pracovníky, aby hlásili jakákoli podezření na nežádoucí účinky na www.sukl.cz/nahlasit-nezadouci-ucinek.

M-CZ-00001237

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

TP53 - I332fs*24 ..... p. 6

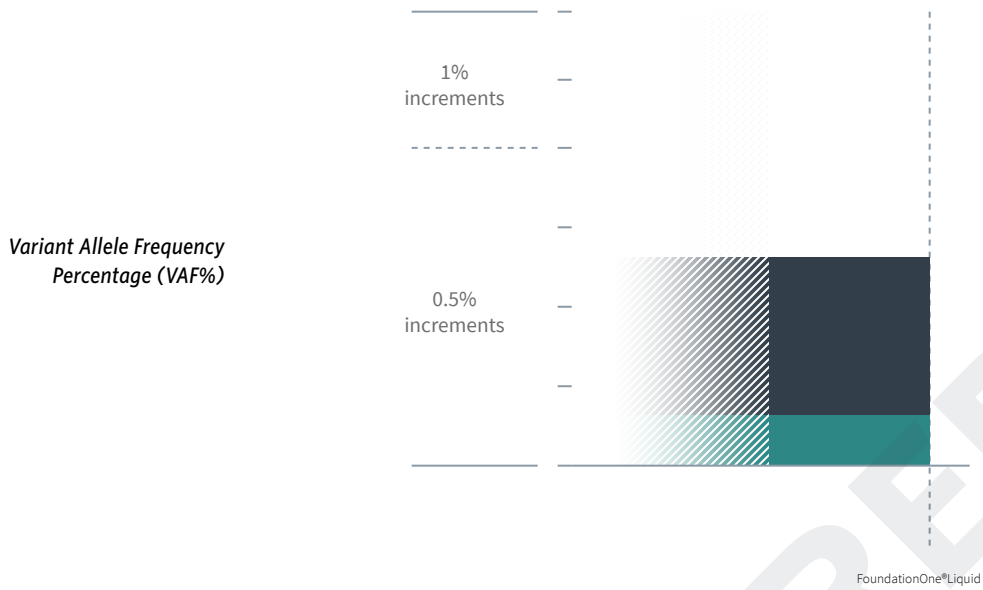
NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally in some EU Member States but may not be available in your Member State: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, and Triptorelin. The Summary of Product Characteristics of EU-approved therapies are available at https://www.ema.europa.eu/en/medicines. The information available on EMA's website is updated in regular intervals but may not reflect the current status at any time. In the appropriate clinical context, germline testing of *APC*, *BRCA1*, *BRCA2*, *BRIP1*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF2*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz



HISTORIC PATIENT FINDINGS		VAF%
Blood Tumor Mutational Burden		6 Muts/Mb
Microsatellite status		Cannot Be Determined
Tumor Fraction		Cannot Be Determined
NF1	● S892fs*10	0.99%
ROS1	CD74-ROS1 fusion	0.38%
TP53	● I332fs*24	0.32%

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

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

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

GENOMIC SIGNATURE

Blood Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

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]. Published data investigating the prognostic implications of bTMB levels in lung cancer are limited (PubMed, Jul 2020). 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)[5]. 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[6]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[6-7].

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[8-9] and cigarette smoke in lung cancer[10-11], treatment with temozolomide-based chemotherapy in glioma[12-13], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[14-18], and microsatellite instability (MSI)[14,17-18]. This sample harbors a bTMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3].

GENOMIC SIGNATURE

Tumor Fraction

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

There are currently no targeted approaches to address specific tumor fraction levels; however, on the basis of emerging clinical evidence, changes in tumor fraction may correlate with treatment duration and clinical response and may be a useful indicator for cancer management[19-24].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels has been reported in a variety of tumor types, with higher tumor fraction levels reported in patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[25]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[26], Ewing sarcoma and osteosarcoma[27], prostate cancer[22], breast cancer[28], leiomyosarcoma[29], esophageal cancer[30], colorectal cancer[31], and gastrointestinal cancer[32].

FINDING SUMMARY

Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. Tumor cells in most advanced solid tumor types may shed ctDNA through the process of apoptosis or necrosis[25,33-34]. Tumor fraction has been proposed to be a noninvasive surrogate biomarker of disease burden dynamics. Elevated tumor fraction levels have been associated with inferior prognosis, and therapeutic resistance to treatment in certain tumor types[22,28,31], whereas reduced levels have been correlated with tumor shrinkage and improved clinical outcome in patients with non-small cell lung cancer, urothelial cancer, and melanoma treated with immunotherapy[20,24,35]. Tumor fraction estimate is computationally derived from observed aneuploid instability in the sample. However, the tumor fraction estimate in this sample could not be determined with confidence.

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

GENE
NF1

ALTERATION
S892fs*10

TRANSCRIPT ID
NM_001042492

CODING SEQUENCE EFFECT
2674delA

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in neurofibromatosis type 1[36-37] and neurofibromatosis-associated glioma or glioblastoma[38-39], as well as extensive preclinical evidence in several tumor types[40-45], 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 the approved agents everolimus and temsirolimus, based on limited clinical data[46-48] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[49-50]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[51]. 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[52], 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[53].

FREQUENCY & PROGNOSIS

In the TCGA datasets, NF1 mutation has been observed in 11% of lung adenocarcinoma cases[54] and 8% of lung squamous cell carcinoma cases[55]. Published data investigating the prognostic implications of NF1 alteration in lung cancer are limited (PubMed, Feb 2020). 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[56].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[57]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[58]. NF1 alterations that result in loss or disruption of the GAP-related domain[59-62], as observed here, are predicted to be inactivating[58,62-67]. 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[68-70]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[71-72], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
ROS1

ALTERATION
CD74-ROS1 fusion

POTENTIAL TREATMENT STRATEGIES

The ROS1 TKIs crizotinib[73], entrectinib[74], ceritinib[75], and lorlatinib[76-77] have shown significant clinical activity for patients with ROS1-rearranged NSCLC. Treatment with either brigatinib[78] or cabozantinib[79-82] has resulted in clinical benefit for patients with ROS1-rearranged NSCLC that developed resistance to crizotinib and ceritinib. Two Phase 1 studies of repotrectinib reported ORRs of 80% (8/10)[83] and 81.8% (9/11)[84] for patients with TKI-naive ROS1-rearranged non-small cell lung cancer (NSCLC); the ORRs for patients previously treated with TKIs were lower (17.6% [3/17] and 38.9% [7/18])[83-84] , and 1 study reported a shorter duration of response than in the first-line setting (10.2 months vs. not reached)[84]. A Phase 1 study of taletrectinib for Japanese patients with ROS1-rearranged NSCLC reported an ORR of 58.3% (7/12) and a DCR of 100% for the overall cohort; ORR was 66.7% (6/9) for crizotinib-naive patients[85]. In a separate Phase 1 study of taletrectinib for patients with advanced solid tumors, the ORR was 33.3% (2/6) and median PFS was 4.1 months for patients with ROS1-rearranged NSCLC who had progressed on crizotinib[86].

FREQUENCY & PROGNOSIS

ROS1 rearrangements or fusions have been reported in 1-2% of non-small cell lung carcinoma (NSCLC) tumors[87-90], including in 1-3.4% of lung adenocarcinoma cases[89,91-94]. CD74-ROS1 fusions accounted for 23% (3/13) to 27% (5/18) of the ROS1 rearrangements identified in two studies of lung cancer[88,92]. Elevated ROS1 protein levels have been observed in 22% of NSCLC samples evaluated in one study[95]. A study of 1,137 patients with lung adenocarcinoma showed that Stage 4 patients with ROS1 rearrangement had significantly better overall survival (OS) compared to other genetically defined Stage 4 subgroups, with an estimated mean OS of 5.3 years for patients who were treated with chemotherapy and crizotinib[90]. Positive kinase fusion status (ALK, ROS1, or RET) was associated with improved prognosis in lung adenocarcinoma, independently of other prognostic factors[88], although never-smokers with surgically resected lung adenocarcinoma and ALK or ROS1 fusion had significantly shorter disease-free survival (hazard ratio, 2.11)[94]. A study of 208 never-smokers observed an improved objective response rate and longer median progression-free survival (PFS) for ROS-fusion-positive patients treated with pemetrexed but a reduced PFS for ROS1-positive patients treated with EGFR-targeted kinase inhibitors[93].

FINDING SUMMARY

The ROS1 oncogene encodes a tyrosine kinase of the insulin receptor family that plays a role in regulating cellular growth and differentiation by activating several signaling pathways, including those involving mitogen-activated protein kinase ERK1/2, phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), STAT3, and VAV3[96]. ROS1 fusions involving the kinase domain of ROS1 (exons 36-42), as seen here, have been characterized as activating and oncogenic[87-89,92,95-111]. Patients with non-small cell lung cancer (NSCLC) and activating ROS1 fusions have experienced clinical benefit from crizotinib[112-114].

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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
I332fs*24

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
955_956insAGAAGAAACCACTGGATGGAGAATATTTCACCC
TTCAGGTACTAAGTCTCGGGACCTC

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[115-118], or p53 gene therapy and immunotherapeutics such as SGT-53[119-123] and ALT-801[124]. 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) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[125]. 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 in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[126]. 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 in patients with platinum-refractory TP53-mutated ovarian cancer[127]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[128]. 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[129]. 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[130]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in 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[123]. 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[131]. 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[132-133]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[134-135]. 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)[54-55,136-141], including 38-54% of lung adenocarcinomas and 47-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Sep 2020)[54-55,142-143]. 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[144]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[99]. Variants seen in this gene have been reported to occur in clonal hematopoiesis of indeterminate potential (CHIP), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[145-150]. CHIP is associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[145-146]. Clinical management of patients with CHIP may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[151]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CHIP[149,152-153]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CHIP.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[154]. Alterations that have been functionally characterized as inactivating and/or result in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, are thought to dysregulate the transactivation of p53-dependent genes and are predicted to promote tumorigenesis[155-159]. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[160-162], including sarcomas[163-164]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[165] to 1:20,000[164]. 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[166]. In the appropriate clinical context, germline testing of TP53 is recommended.

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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

Brigatinib

Assay findings association

ROS1
CD74-ROS1 fusion

AREAS OF THERAPEUTIC USE

Brigatinib is a kinase inhibitor that targets ALK, ROS1, and mutated EGFR and is available in the EU to treat patients with metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical responses in patients with ROS1-fusion-positive NSCLC[78,167] and strong preclinical evidence[168-169] , ROS1 rearrangements may predict sensitivity to brigatinib.

SUPPORTING DATA

Brigatinib has been studied primarily for the treatment of ALK-rearranged NSCLC[170-172] . Brigatinib was associated with an ORR of 17% (3/18 patients) in other solid tumors with ALK/ROS1/EGFR alterations[78]. A patient with ROS1-rearranged non-small cell lung cancer (NSCLC) that had previously progressed on crizotinib and then ceritinib exhibited a PR following treatment with brigatinib[167]. In another study for 3 patients with NSCLC and ROS1 rearrangements treated with brigatinib, 2 previously treated with crizotinib experienced SD and PD, whereas the single patient who was crizotinib-naive experienced a PR lasting >21 months[78]. A case study of 4 patients with ROS1-rearranged NSCLC who had progressed on crizotinib reported a 25% (1/4) ORR[173].

Ceritinib

Assay findings association

ROS1
CD74-ROS1 fusion

AREAS OF THERAPEUTIC USE

Ceritinib is an inhibitor of the kinases ALK, ROS1, IR, and IGF-1R. It is available in the EU to treat advanced ALK-positive non-small cell lung carcinoma (NSCLC) either as first-line treatment or following crizotinib therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of Phase 2 clinical studies demonstrating benefit to patients with ROS1-rearranged NSCLC[75,174] , ROS1 rearrangements may predict sensitivity to ceritinib.

SUPPORTING DATA

Ceritinib has been shown to confer clinical benefit in patients with ALK/ROS1-rearranged NSCLC[75,175] . In a Phase 2 study for patients with advanced ROS1-rearranged NSCLC, ceritinib achieved an ORR of 67% (20/30) and a median progression-free survival of 19.3 months for crizotinib-naive patients[75]. The median OS among all patients was 24 months, and 5/8 (63%) patients with brain metastases experienced intracranial disease control[75]. Another Phase 2 study of ceritinib treatment in ALK- or ROS1-rearranged advanced lung adenocarcinoma reported confirmed PRs in 73% (19/26) of patients, a DCR of 92% (24/26), and a median PFS of 14.4 months[174]. In patients with ROS1-rearranged NSCLC that have progressed on crizotinib, the clinical evidence for ceritinib is limited and mixed[75,176-177] . Among the two patients previously treated with crizotinib included in a Phase 2 study of ceritinib, neither responded to treatment[75]; however, in a separate case study, a patient with ROS1-rearranged NSCLC that progressed on crizotinib was treated with ceritinib and exhibited a PR for 8 months before a pause due to toxicity followed by an additional 17 months of clinical benefit when ceritinib was resumed[167,177] .

Crizotinib

Assay findings association

ROS1
CD74-ROS1 fusion

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is available in the EU to treat patients with advanced non-small cell lung cancer (NSCLC) whose tumors are positive for ALK either as first-line or following previous treatment. It is also available to treat patients with ROS1-positive advanced NSCLC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Crizotinib has shown clinical and preclinical evidence of activity in ROS1-rearranged NSCLC[73,89-90,92,113-114,178-183] and IMT[100].

SUPPORTING DATA

Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[184-188] , ROS1 rearrangements[90,113-114,189-190] , an NTRK1 fusion[191], or MET activation[192-208] . The Phase 2 METROS trial for pretreated patients with ROS1-rearranged NSCLC treated with crizotinib reported an ORR of 65% (n=26; 1 CR, 16 PRs, 6 SDs), and with median follow-up of 21 months, median PFS was 22.8 months and median OS was not reached[209]. Similarly, the Phase 1 PROFILE 1001 trial for patients with ROS1-rearranged NSCLC treated with crizotinib reported an ORR of 72% (n= 53; 6 CRs, 32 PRs and 10 SD)[73]. High ORR to crizotinib in ROS1-rearranged NSCLC is observed in other studies[189-190] . In the AcSé trial, patients with ROS1-translocated NSCLC treated with crizotinib achieved an ORR of 67.6% (1 CR and 24 PRs) and a DCR of 86% (32/37) with a median PFS and OS of 5.5 months and 17.2 months, respectively[189]. In retrospective studies, crizotinib therapy was associated with an ORR of 80% (24/30) or higher (5/5) and a median PFS of 9.1 months for patients with ROS1-rearranged advanced lung adenocarcinoma[90,114] .

Entrectinib

Assay findings association

ROS1
CD74-ROS1 fusion

AREAS OF THERAPEUTIC USE

Entrectinib is a TKI that targets TRKA/B/C (NTRK1/2/3), ROS1, and ALK. It is available in the EU to treat patients with ROS1-positive non-small cell lung cancer (NSCLC) and patients with NTRK fusion-positive solid tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[74,210-212] and clinical benefit in other solid tumor types[213-216] , ROS1 fusions may predict sensitivity to entrectinib.

SUPPORTING DATA

Combined analysis of Phase 1 and Phase 2 trials of entrectinib in ROS1-inhibitor-naive NSCLC with ROS1 gene fusion with and without CNS metastases reported an ORR of 77.4% (41/53, 3 CRs), a median response duration of 24.6 months, and a median PFS of 19.0 months[217]. The ORR was similar for patients with (73.9%, 17/23) and without (80.0%, 24/30) CNS disease at baseline, and the intracranial ORR was 55.0% (11/20)[217]. A real-world study in ROS1-rearranged NSCLC reported median PFS of 19.0 and 8.5 months to entrectinib and crizotinib, respectively[210]. Clinical benefit with entrectinib monotherapy has been achieved for adult and pediatric patients with various solid tumors with and without CNS metastases and with NTRK, ROS1, or ALK fusions[74,210-213,218] , and preclinical sensitivity has been observed in NTRK fusion-positive AML cell lines[219]. In a Phase 1 trial, responses were restricted to patients harboring NTRK, ROS1, or ALK rearrangements, with the exception of ALK-mutant neuroblastoma, and were observed for patients with ALK or ROS1 rearrangements who had not received prior ALK TKI or crizotinib, respectively[74].

Lorlatinib

Assay findings association

ROS1
CD74-ROS1 fusion

AREAS OF THERAPEUTIC USE

Lorlatinib is a TKI that targets ALK and ROS1. It is available in the EU to treat patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) following disease progression after first-line ALK TKI therapy with alectinib or ceritinib or after crizotinib and at least one other ALK TKI. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[76-77,220-223] and preclinical[223-225] evidence, ROS1 activation may predict sensitivity to lorlatinib.

SUPPORTING DATA

Lorlatinib has primarily been investigated for ALK- and ROS1-positive NSCLC as an approach to overcome resistance to prior TKIs[76,226] . A Phase 1 study evaluating lorlatinib for the treatment of NSCLC reported an ORR of 50% (6/12) and a median duration of response (mDOR) of 12 months for ROS1-positive patients[76]. In the follow-up Phase 2 trial, patients who were crizotinib-naive and -treated achieved ORRs of 62% (13/21; 2 CRs, 11 PRs) and 35% (14/40; 2 CRs, 12 PRs) and a mPFS of 21 and 8.5 months, respectively; intracranial (IC) activity was seen irrespective of prior treatment, with crizotinib-naive and -treated patients achieving an IC-ORR of 64% (7/11; 5 CRs, 2 PRs) and 50% (12/24; 9 CRs, 3 PRs), respectively[77]. In case studies, a patient with metastatic NSCLC harboring an EZR–ROS1 fusion and S1986Y/F dual mutations responded to lorlatinib[223], and a patient with lung adenocarcinoma and EZR-ROS1 fusion experienced a PR from second-line crizotinib and an ongoing reduction in serum CEA from third-line lorlatinib[221].

Trametinib

Assay findings association

NF1
S892fs*10

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is available in the EU as monotherapy or in combination with dabrafenib to treat unresectable or metastatic melanoma with a BRAF V600 mutation as well as in combination with dabrafenib as adjuvant treatment for completely resected advanced BRAF V600-mutated melanoma. It is also available in combination with dabrafenib to treat patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[36,39] and strong preclinical evidence[41-45] , 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[227]. 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[228]. 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[229-231] . 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[232-234] . 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[235]. 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[236-238] . 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[239]. 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[52], 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[53].

Binimetinib

Assay findings association

NF1
S892fs*10

AREAS OF THERAPEUTIC USE

Binimetinib is a MEK inhibitor that is available in the EU in combination with encorafenib to treat patients with unresectable or metastatic melanoma with a BRAF V600E mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[36,39] and strong preclinical evidence[40-45] , NF1 inactivation may predict sensitivity to MEK inhibitors such as binimetinib.

SUPPORTING DATA

In the Phase 2 CLUSTER study, treatment with single-agent binimetinib resulted in a PR rate of 9% (2/22) and a DCR of 59% (13/22) in patients with KRAS-, NRAS-, or BRAF-mutated advanced lung adenocarcinoma[174]. A case study observed improved responses in leptomeningeal and brain metastases for a patient with BRAF V600E-mutated lung adenocarcinoma following combination treatment with encorafenib and binimetinib[240]. Patients with various solid tumors have benefited from binimetinib as a monotherapy or in combination with other agents. In the Phase 3 COLUMBUS trial, patients with BRAF V600-mutated melanoma achieved superior benefit from addition of binimetinib to the BRAF inhibitor encorafenib (ORR 64%, PFS 14.9 months, OS 33.6 months) compared with encorafenib alone (ORR 52%, PFS 9.6 months, OS 23.5 months)[241-242] . The Phase 3 NEMO trial for patients with NRAS-mutated melanoma reported marginally increased ORR and PFS with no significant OS benefit for binimetinib monotherapy (ORR 15%, PFS 3 months, OS 11 months) compared with dacarbazine (ORR 7%, PFS 1.8 months, OS 10.1 months)[243]. Single-arm and retrospective studies have suggested intracranial activity of binimetinib alone or combined with encorafenib for NRAS- or BRAF-mutated metastatic melanoma[244-245] . The Phase 3 BEACON study for patients with BRAF V600E-mutated colorectal cancer showed that triplet therapy of binimetinib with encorafenib and the EGFR-targeting antibody cetuximab significantly improved median OS (9.0 vs. 5.4 months, HR=0.52) and ORR (26% vs. 2%) relative to the standard irinotecan and cetuximab therapy[246]. For patients with low-grade serous ovarian carcinoma, the Phase 3 MILO study of binimetinib versus physician's choice chemotherapy reported no significant improvement in median PFS (9.1 vs. 10.6 months) and did not meet its primary end point[247]. Although single-agent binimetinib has had limited efficacy in biliary tract cancer[248-249] , Phase 1/2 studies have evaluated binimetinib combined with gemcitabine and cisplatin in previously untreated patients (ORR 36%, DCR 74%, PFS 6.0 months, OS 13.3 months)[250] or binimetinib combined with capecitabine in patients with progression on gemcitabine (ORR 21%, DCR 76%, PFS 4.1 months, OS 7.8 months)[251]. In early phase studies, objective responses have been reported for patients with various KRAS-, NRAS-, or BRAF-mutated solid tumor types, including lung, thyroid, uterine, and ovarian cancer, who were treated with binimetinib as a single agent[174,252] or in combination with other therapies[253-256] .

Cabozantinib

Assay findings association

ROS1
CD74-ROS1 fusion

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is available in the EU to treat advanced renal cell carcinoma (RCC) as first-line therapy for patients with intermediate- or poor-risk RCC or following prior antiangiogenic therapy. It is also available to treat progressive, unresectable, advanced medullary thyroid carcinoma (MTC), and as monotherapy for the treatment of hepatocellular carcinoma (HCC) after prior treatment with sorafenib. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Cabozantinib has shown clinical efficacy in ROS1-rearranged NSCLC after disease progression on at least one prior ROS1 TKI[79-82,257] and preclinical activity in wild-type and mutant ROS1-fusion cell lines[79-80,168,258] .

SUPPORTING DATA

A Phase 2 study of cabozantinib for ROS1-rearranged lung adenocarcinoma previously treated with at least 1 ROS1 TKI reported 1 PR lasting 9.1 months until resistance due to an emergent MET D1228N mutation, 1 unconfirmed PR, and 4 SDs[257]. Other case studies of patients with ROS1-rearranged NSCLC previously treated with at least 1 ROS1 TKI have reported 4 PRs[79-82] , 3 SDs (duration of 2.2–7.4 months)[81], and 1 PD[259]. A Phase 2 randomized discontinuation trial of cabozantinib reported a 10.0% (6/60) ORR and a 58.3% (35/60) DCR, with median PFS of 4.2 months, for patients with genomically unselected, heavily pretreated NSCLC[260]. Patients with EGFR wild-type non-squamous NSCLC who had progressed after previous treatment experienced longer median PFS with cabozantinib alone or combined with erlotinib (4.3 and 4.7 months, HR=0.39 and 0.37, respectively) compared with single agent erlotinib (1.8 months) in a randomized Phase 2 trial[261]. A Phase 1 study of cabozantinib for advanced solid tumors reported an ORR of 20.0% (4/20; 4 PRs, all in EGFR-mutated tumors) and DCR of 100% (20/20) in the expansion cohort for Japanese patients with NSCLC[262].

Cobimetinib

Assay findings association

NF1
S892fs*10

AREAS OF THERAPEUTIC USE

Cobimetinib is a MEK inhibitor. It is available in the EU in combination with vemurafenib to treat unresectable or metastatic melanoma with a BRAF V600 mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[36,39] and strong preclinical evidence[41-45] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of cobimetinib for the treatment of non-small cell lung cancer are limited (PubMed, Sep 2020). Cobimetinib has been investigated primarily in combination with vemurafenib for the treatment of patients with BRAF V600-mutated melanoma. In the Phase 3 coBRIM study, patients with V600-mutated melanoma treated with the BRAF inhibitor vemurafenib plus cobimetinib reported improved ORR (67.6% vs. 44.7%), median OS (22.3 months vs. 17.4 months; HR=0.70), and median PFS (9.9 months vs. 6.2 months; HR=0.51) compared with vemurafenib alone[263-264] . Single-agent cobimetinib has shown clinical activity in the context of histiocytosis (ORR of 64.3%, 9/14)[265]. The Phase 2 COLET study comparing first-line cobimetinib in combination with paclitaxel to paclitaxel alone for the treatment of patients with advanced triple-negative breast cancer reported numerically higher ORR (38.3% [18/47] vs. 20.9% [9/43]) and improved median PFS (5.5 vs. 3.8 months, HR=0.73)[266]. Additional cohorts from the COLET study treated with triple combinations of cobimetinib, atezolizumab, and either paclitaxel or nab-paclitaxel showed ORRs of 34.4% (11/32) or 29.0% (9/31), respectively, with numerically higher ORRs and PFS reported for patients with PD-L1 expression[267]. A Phase 1b study evaluating atezolizumab in combination with cobimetinib for advanced solid tumors reported an ORR of 8.3% (7/84) for patients with CRC, 40.9% (9/22) for patients with melanoma, 17.9% (5/28) for patients with NSCLC, and 18.8% (3/16) for patients with other tumors (ovarian cancer, clear cell sarcoma, and renal cell carcinoma); there was no association between BRAF or KRAS mutation status and response rate in any disease setting[268-269] . In a Phase 1b study of cobimetinib and the AKT inhibitor ipatasertib, 3/47 patients with KRAS-mutated ovarian, mesonephric cervical, or endometrial carcinoma had a PR[270].

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

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
NF1

ALTERATION
S892fs*10

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.

NCT03745989

PHASE 1

Study of MK-8353 + Selumetinib in Advanced/Metastatic Solid Tumors (MK-8353-014)

TARGETS
ERK1, ERK2, MEK

LOCATIONS: Bellinzona (Switzerland), Toronto (Canada), Florida, Vancouver (Canada), Texas

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, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03989115

PHASE 1/2

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

TARGETS
SHP2, MEK

LOCATIONS: Massachusetts, Pennsylvania, Maryland, Virginia, Michigan, Ohio, Illinois, Wisconsin, North Carolina, Tennessee

CLINICAL TRIALS

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL2, BCL-XL, BCL-W

LOCATIONS: New York, New Jersey, Maryland

NCT03600701

PHASE 2

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

TARGETS
PD-L1, MEK

LOCATIONS: District of Columbia, Virginia, Ohio, Florida, California

NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

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

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada), Florida, Texas

NCT03225664

PHASE 1/2

BATTLE-2 Program - A Biomarker-Integrated Targeted Therapy in Non-Small Cell Lung Cancer (NSCLC)

TARGETS
PD-1, MEK

LOCATIONS: Texas

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

GENE
ROS1

RATIONALE
Activating ROS1 fusions may predict sensitivity to inhibitors of ROS1.

ALTERATION
CD74-ROS1 fusion

NCT02568267

PHASE 2

Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Padova (Italy), Milano (Italy), Pisa (Italy), Candiolo (Italy), Perugia (Italy), Roma (Italy), Heidelberg (Germany), Lyon (France), Marseille (France), Marseille cedex 5 (France)

NCT03178552

PHASE 2/3

A Study to Evaluate Efficacy and Safety of Multiple Targeted Therapies as Treatments for Participants With Non-Small Cell Lung Cancer (NSCLC)

TARGETS
ALK, RET, PD-L1, BRAF, MEK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Cremona (Italy), Bergamo (Italy), Monza (Italy), Milano (Italy), Aviano (Italy), Meldola (Italy), Orbassano (TO) (Italy), Gauting (Germany), Esslingen (Germany), Gerlingen (Germany)

NCT03093116

PHASE 1/2

A Study of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Milan (Italy), Terni (Italy), Heidelberg (Germany), Marseille (France), Dresden (Germany), Cologne (Germany), Villejuif (France), Berlin (Germany), Barcelona (Spain), Amsterdam (Netherlands)

NCT03439215

PHASE 2

PF-06463922 for Crizotinib Pretreated ROS1 Positive Non-small-cell Lung Cancer

TARGETS
ROS1, ALK

LOCATIONS: Milano (Italy), Ravenna (Italy), Perugia (Italy)

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, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

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.

ATM K1440R	***BRCA1*** S377G	***BRCA2*** K3326*	***CBL*** M374L and S739F
CHEK2 I160T	***CSF3R*** Q245L	***CUL3*** R756Q	***EGFR*** V904I
KLHL6 E535fs*1	***MST1R*** F164L	***NOTCH2*** P2189A	***ROS1*** W2198fs*26

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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 Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

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.

ATM K1440R	***BRCA1*** S377G	***BRCA2*** K3326*	***CBL*** M374L and S739F
CHEK2 I160T	***CSF3R*** Q245L	***CUL3*** R756Q	***EGFR*** V904I
KLHL6 E535fs*1	***MST1R*** F164L	***NOTCH2*** P2189A	***ROS1*** W2198fs*26

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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 Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

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)
KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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 Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

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.

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*	*WTI*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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 Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

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

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and 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 detects select genomic rearrangements, select copy number alterations, tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

THE REPORT

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF ALTERATIONS AND THERAPIES

Genomic Signatures and Gene Alterations
Therapies are ranked based on the following criteria: Therapies approved in the EU in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies approved in the EU in another tumor type (ranked alphabetically within each NCCN category).

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 in the patient's tumor.
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 observed aneuploid instability in the sample.
9. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Genomic signatures and gene alterations detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each genomic signature or gene alteration. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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 Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz

Guidelines®). © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

SELECT ABBREVIATIONS

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

PDF Service Version 2.16.1

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. Xiao D, et al. Oncotarget (2016) pmid: 27009843
6. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
7. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
8. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
9. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
10. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
11. Rizvi NA, et al. Science (2015) pmid: 25765070
12. Johnson BE, et al. Science (2014) pmid: 24336570
13. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
14. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
15. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
16. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
17. Nature (2012) pmid: 22810696
18. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
19. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
20. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
21. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
22. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
23. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
24. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
25. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
26. Lapin M, et al. J Transl Med (2018) pmid: 30400802
27. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
28. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
29. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
30. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
31. Fan G, et al. PLoS ONE (2017) pmid: 28187169
32. Vu et al., 2020; DOI: 10.1200/PO.19.00204
33. Snyder MW, et al. Cell (2016) pmid: 26771485
34. Stroun M, et al. Clin. Chim. Acta (2001) pmid: 11694251
35. Lipson EJ, et al. J Immunother Cancer (2014) pmid: 25516806
36. Dombi E, et al. N. Engl. J. Med. (2016) pmid: 28029918
37. Gross AM, et al. N. Engl. J. Med. (2020) pmid: 32187457
38. Fangusaro J, et al. Lancet Oncol. (2019) pmid: 31151904
39. Ameratunga M, et al. J Clin Pharm Ther (2016) pmid: 26936308
40. Woodfield SE, et al. BMC Cancer (2016) pmid: 26925841
41. Jousma E, et al. Pediatr Blood Cancer (2015) pmid: 25907661
42. Nissan MH, et al. Cancer Res. (2014) pmid: 24576830
43. Jessen WJ, et al. J. Clin. Invest. (2013) pmid: 23221341
44. Chang T, et al. J. Clin. Invest. (2013) pmid: 23221337
45. See WL, et al. Cancer Res. (2012) pmid: 22573716
46. Lim SM, et al. Oncotarget (2016) pmid: 26859683
47. Weiss B, et al. Neuro-oncology (2015) pmid: 25314964
48. Janku F, et al. Oncotarget (2014) pmid: 24931142
49. Johannessen CM, et al. Curr. Biol. (2008) pmid: 18164202
50. Johannessen CM, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15937108
51. Malone CF, et al. Cancer Discov (2014) pmid: 24913553
52. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
53. Patterson et al., 2018; AACR Abstract 3891
54. Nature (2014) pmid: 25079552
55. Nature (2012) pmid: 22960745
56. de Bruin EC, et al. Cancer Discov (2014) pmid: 24535670
57. Hattori S, et al. Biochem. Biophys. Res. Commun. (1991) pmid: 1904223
58. Morcos P, et al. Mol. Cell. Biol. (1996) pmid: 8628317
59. Ballester R, et al. Cell (1990) pmid: 2121371
60. Xu GF, et al. Cell (1990) pmid: 2116237
61. Martin GA, et al. Cell (1990) pmid: 2121370
62. Thomas L, et al. Hum. Mutat. (2012) pmid: 22807134
63. Skuse GR, et al. Hum. Mol. Genet. (1997) pmid: 9300663
64. Messiaen LM, et al. Genet. Med. () pmid: 11258625
65. Ars E, et al. Hum. Mol. Genet. (2000) pmid: 10607834
66. Messiaen LM, et al. J. Med. Genet. (2005) pmid: 15863657
67. Poullet P, et al. Mol. Cell. Biol. (1994) pmid: 8264648
68. Jett K, et al. Genet. Med. (2010) pmid: 20027112
69. Patil S, et al. Oncologist (2012) pmid: 22240541
70. Evans DG, et al. Clin Sarcoma Res (2012) pmid: 23036231
71. Upadhyaya M, et al. J. Med. Genet. (1995) pmid: 8544190
72. Williams VC, et al. Pediatrics (2009) pmid: 19117870
73. Shaw AT, et al. Ann. Oncol. (2019) pmid: 30980071
74. Drilon A, et al. Cancer Discov (2017) pmid: 28183697
75. Lim SM, et al. J. Clin. Oncol. (2017) pmid: 28520527
76. Shaw AT, et al. Lancet Oncol. (2017) pmid: 29074098
77. Shaw AT, et al. Lancet Oncol. (2019) pmid: 31669155
78. Gettinger SN, et al. Lancet Oncol. (2016) pmid: 27836716
79. Chong CR, et al. Clin. Cancer Res. (2017) pmid: 27370605
80. Drilon A, et al. Clin. Cancer Res. (2016) pmid: 26673800
81. Sun TY, et al. J Thorac Oncol (2019) pmid: 30217491
82. Zugazagoitia J, et al. Lung Cancer (2019) pmid: 31319999
83. Lin et al., 2018; WCLC Abstract OA02.02
84. Cho et al., 2019; ASCO Abstract 9011
85. Fujiwara Y, et al. Oncotarget (2018) pmid: 29805770
86. Papadopoulos KP, et al. Clin. Cancer Res. (2020) pmid: 32591465
87. Shaw AT, et al. Nat. Rev. Cancer (2013) pmid: 24132104
88. Takeuchi K, et al. Nat. Med. (2012) pmid: 22327623
89. Davies KD, et al. Clin. Cancer Res. (2012) pmid: 22919003
90. Scheffler M, et al. Oncotarget (2015) pmid: 25868855
91. Pan Y, et al. Lung Cancer (2014) pmid: 24629636
92. Bergethon K, et al. J. Clin. Oncol. (2012) pmid: 22215748
93. Kim HR, et al. Ann. Oncol. (2013) pmid: 23788756
94. Kim MH, et al. Lung Cancer (2014) pmid: 24462463
95. Lee HJ, et al. Ann. Surg. Oncol. (2013) pmid: 22915320
96. Acquaviva J, et al. Biochim. Biophys. Acta (2009) pmid: 18778756
97. Lovly et al., 2013; ASCO Abstract 10513
98. Jun HJ, et al. Cancer Res. (2012) pmid: 22659450
99. Seo JS, et al. Genome Res. (2012) pmid: 22975805
100. Lovly CM, et al. Cancer Discov (2014) pmid: 24875859
101. Charest A, et al. Cancer Res. (2006) pmid: 16885344
102. Saborowski A, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 24154728
103. Giacomini CP, et al. PLoS Genet. (2013) pmid: 23637631
104. Mescam-Mancini L, et al. Lung Cancer (2014) pmid: 24380695
105. Rikova K, et al. Cell (2007) pmid: 18083107
106. Davies KD, et al. Clin. Cancer Res. (2013) pmid: 23719267
107. Lee J, et al. Cancer (2013) pmid: 23400546
108. Hernández L, et al. Am. J. Pathol. (2002) pmid: 11943732
109. Hernández L, et al. Blood (1999) pmid: 10556217
110. Ou SH, et al. Lung Cancer (2015) pmid: 25851827
111. Lawrence B, et al. Am. J. Pathol. (2000) pmid: 10934142
112. Li H, et al. J. Cancer Res. Clin. Oncol. (2015) pmid: 25230898
113. Shaw AT, et al. N. Engl. J. Med. (2014) pmid: 25264305
114. Mazières J, et al. J. Clin. Oncol. (2015) pmid: 25667280
115. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
116. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
117. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
118. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
119. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
120. Xu L, et al. Mol. Med. (2001) pmid: 11713371
121. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
122. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
123. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
124. Hajdenberg et al., 2012; ASCO Abstract e15010
125. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
126. Moore et al., 2019; ASCO Abstract 5513
127. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
128. Oza et al., 2015; ASCO Abstract 5506
129. Lee J, et al. Cancer Discov (2019) pmid: 31315834
130. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
131. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
132. Kwok M, et al. Blood (2016) pmid: 26563132
133. Boudny M, et al. Haematologica (2019) pmid: 30975914
134. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
135. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
136. Mogi A, et al. J. Biomed. Biotechnol. (2011) pmid: 21331359
137. Tekpli X, et al. Int. J. Cancer (2013) pmid: 23011884
138. Vignot S, et al. J. Clin. Oncol. (2013) pmid: 23630207
139. Maeng CH, et al. Anticancer Res. (2013) pmid: 24222160
140. Cortot AB, et al. Clin Lung Cancer (2014) pmid: 24169260
141. Itakura M, et al. Br. J. Cancer (2013) pmid: 23922113
142. Imielinski M, et al. Cell (2012) pmid: 22980975
143. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
144. Dong ZY, et al. Clin. Cancer Res. (2017) pmid: 28039262
145. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
146. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
147. Xie M, et al. Nat. Med. (2014) pmid: 25326804
148. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
149. Severson EA, et al. Blood (2018) pmid: 29678827
150. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
151. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
152. Chabon JJ, et al. Nature (2020) pmid: 32269342
153. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
154. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
155. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
156. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
157. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
158. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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 Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

159. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
160. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
161. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
162. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
163. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
164. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
165. Lalloo F, et al. Lancet (2003) pmid: 12672316
166. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
167. Hegde et al., 2019; doi: 10.1200/PO.18.00267
168. Davare MA, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 26372962
169. Zhang S, et al. Clin. Cancer Res. (2016) pmid: 27780853
170. Camidge et al., 2016; World Conference on Lung Cancer P3.02a-013
171. Kim DW, et al. J. Clin. Oncol. (2017) pmid: 28475456
172. Camidge DR, et al. N. Engl. J. Med. (2018) pmid: 30280657
173. Dudnik E, et al. Clin Transl Oncol (2020) pmid: 32462394
174. Wu et al., 2018; WCLC Abstract P1.01-97
175. Soria JC, et al. Lancet (2017) pmid: 28126333
176. Dagogo-Jack I, et al. J. Clin. Oncol. (2017) pmid: 28520528
177. Subbiah V, et al. Proc. Natl. Acad. Sci. U.S.A. (2016) pmid: 26917690
178. Ou et al., 2013; ASCO Abstract 8032
179. Komiya T, et al. J. Clin. Oncol. (2012) pmid: 22891268
180. Yasuda H, et al. J Thorac Oncol (2012) pmid: 22617245
181. Moro-Sibilot et al., 2015; ASCO Abstract 8065
182. Li Z, et al. J Thorac Oncol (2018) pmid: 29704675
183. Wu YL, et al. J. Clin. Oncol. (2018) pmid: 29596029
184. Shaw et al., 2016; ASCO Abstract 9066
185. Lu et al., 2016; ASCO Abstract 9058
186. Yoshida T, et al. J. Clin. Oncol. (2016) pmid: 27354483
187. Solomon BJ, et al. N. Engl. J. Med. (2014) pmid: 25470694
188. Shaw AT, et al. N. Engl. J. Med. (2013) pmid: 23724913
189. Moro-Sibilot D, et al. Ann. Oncol. (2019) pmid: 31584608
190. Goto et al., 2016; ASCO Abstract 9022
191. Vaishnavi A, et al. Nat. Med. (2013) pmid: 24162815
192. Drilon et al., 2016; ASCO Abstract 108
193. Vassal et al., 2015; ASCO Abstract 2595
194. Camidge et al., 2014; ASCO Abstract 8001
195. Li et al., 2015; ASCO Abstract 8090
196. Schrock AB, et al. J Thorac Oncol (2016) pmid: 27343443
197. Jorge SE, et al. Lung Cancer (2015) pmid: 26791794
198. Paik PK, et al. Cancer Discov (2015) pmid: 25971939
199. Mahjoubi L, et al. Invest New Drugs (2016) pmid: 26892698
200. Benderra MA, et al. J Thorac Oncol (2016) pmid: 26845121
201. Waqar SN, et al. J Thorac Oncol (2015) pmid: 25898962
202. Mendenhall MA, et al. J Thorac Oncol (2015) pmid: 25898965
203. Jenkins RW, et al. Clin Lung Cancer (2015) pmid: 25769807
204. Awad MM, et al. J. Clin. Oncol. (2016) pmid: 26729443
205. Schwab R, et al. Lung Cancer (2014) pmid: 24192513
206. Zhang Y, et al. J Thorac Oncol (2016) pmid: 26724472
207. Ou SH, et al. J Thorac Oncol (2011) pmid: 21623265
208. Le X, et al. Clin Lung Cancer (2015) pmid: 25922291
209. Landi L, et al. Clin. Cancer Res. (2019) pmid: 31416808
210. Doebele et al., 2019; ASCO Abstract 9070
211. Doebele et al., 2018; WCLC Abstract OA02.01
212. Siena et al., 2019; ASCO Abstract 3017
213. Robinson et al., 2019; ASCO Abstract 10009
214. Pishvaian et al., 2018; doi/full/10.1200/PO.18.00039
215. Couts et al., 2017; DOI: 10.1200/PO.16.00013
216. Ambati et al., 2018; doi/full/10.1200/PO.18.00095
217. Drilon A, et al. Lancet Oncol. (2020) pmid: 31838015
218. Demetri et al., 2018; ESMO Abstract LBA17
219. Smith KM, et al. Mol. Cancer Ther. (2018) pmid: 29237803
220. Ou et al., 2018; WCLC Abstract OA02.03
221. Dong L, et al. BMC Pulm Med (2018) pmid: 29361925
222. Solomon et al., 2018; ESMO Abstract 1380PD
223. Facchinetti F, et al. Clin. Cancer Res. (2016) pmid: 27401242
224. Davare MA, et al. Clin. Cancer Res. (2018) pmid: 30171048
225. Zou HY, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25733882
226. Bauer et al., 2018; WCLC Abstract MA08.05
227. Planchard D, et al. Lancet Oncol. (2016) pmid: 27283860
228. Planchard D, et al. Lancet Oncol. (2017) pmid: 28919011
229. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
230. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
231. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
232. Kelly et al., 2013; ASCO Abstract 8027
233. Gandara et al., 2013; ASCO Abstract 8028
234. Jänne PA, et al. Lancet Oncol. (2013) pmid: 23200175
235. Carter CA, et al. Ann. Oncol. (2016) pmid: 26802155
236. Banerji et al., 2014; ASCO Abstract e13559
237. Castellano E, et al. Cancer Cell (2013) pmid: 24229709
238. Ku BM, et al. Invest New Drugs (2015) pmid: 25342139
239. Bedard PL, et al. Clin. Cancer Res. (2015) pmid: 25500057
240. McLoughlin EM, et al. J Thorac Oncol (2019) pmid: 31757377
241. Dummer R, et al. Lancet Oncol. (2018) pmid: 29573941
242. Ascierto PA, et al. Eur. J. Cancer (2020) pmid: 31901705
243. Dummer R, et al. Lancet Oncol. (2017) pmid: 28284557
244. Goldinger SM, et al. Br. J. Dermatol. (2020) pmid: 31436845
245. Holbrook K, et al. Cancer (2020) pmid: 31658370
246. Kopetz S, et al. N. Engl. J. Med. (2019) pmid: 31566309
247. Grisham et al., 2019; dx.doi.org/10.1136/ijgc-2019-IGCS.1
248. Finn RS, et al. Invest New Drugs (2018) pmid: 29785570
249. Bendell JC, et al. Br. J. Cancer (2017) pmid: 28152546
250. Lowery MA, et al. Clin. Cancer Res. (2019) pmid: 30563938
251. Kim JW, et al. Br. J. Cancer (2019) pmid: 31312030
252. Slosberg ED, et al. Oncotarget (2018) pmid: 29765547
253. Bardia A, et al. Oncologist (2020) pmid: 31395751
254. Grisham R, et al. Clin. Cancer Res. (2018) pmid: 29844129
255. Ascierto et al., 2017; ASCO Abstract 9518
256. Kefford et al., 2013; Melanoma Bridge Meeting Abstract P5
257. Guo et al., 2019; WCLC 2019
258. Katayama R, et al. Clin. Cancer Res. (2015) pmid: 25351743
259. Guisier F, et al. Clin Lung Cancer (2019) pmid: 31395437
260. Hellerstedt BA, et al. Clin Lung Cancer (2019) pmid: 30528315
261. Neal JW, et al. Lancet Oncol. (2016) pmid: 27825638
262. Nokihara H, et al. Clin Lung Cancer (2019) pmid: 30718102
263. Larkin J, et al. N. Engl. J. Med. (2014) pmid: 25265494
264. Ascierto PA, et al. Lancet Oncol. (2016) pmid: 27480103
265. Diamond EL, et al. Nature (2019) pmid: 30867592
266. Brufsky et al., 2017; SABCS Abstract P5-21-01
267. Brufsky et al., 2019; ASCO Abstract 1013
268. Hellmann MD, et al. Ann. Oncol. (2019) pmid: 30918950
269. Bendell et al., 2016; ASCO Abstract 3502
270. Bendell et al., 2014; AACR Abstract CT328

Electronically signed by Mirna Lechpammer, M.D., Ph.D. | 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 Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Roche s.r.o., Futurama Business Park Bld F, Sokolovská 685/136f, 186 00 Praha 8
tel.: +420 220 382 111, fax: +420 220 382 138, e-mail: prague.info@roche.com, www.roche.cz