

**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

18 Clinical Trials

0 Therapies with Lack of Response

**GENOMIC SIGNATURES**

**Blood Tumor Mutational Burden** - 6 Muts/Mb

**Microsatellite status** - Cannot Be Determined

**Tumor Fraction** - Cannot Be Determined

**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.

**GENE ALTERATIONS**

**VAF %**

**ROS1** - CD74-ROS1 fusion 0.38%

10 Trials see p. 14

**NF1** - S892fs\*10 0.99%

10 Trials see p. 12

**THERAPIES APPROVED IN THE EU  
(IN PATIENT'S TUMOR TYPE)**

Ceritinib 2A  
Crizotinib 2A  
Entrectinib 2A  
Lorlatinib 2A  
Brigatinib

Trametinib

**THERAPIES APPROVED IN THE EU  
(IN OTHER TUMOR TYPE)**

Cabozantinib

Binimetinib

Cobimetinib

☐ NCCN category

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

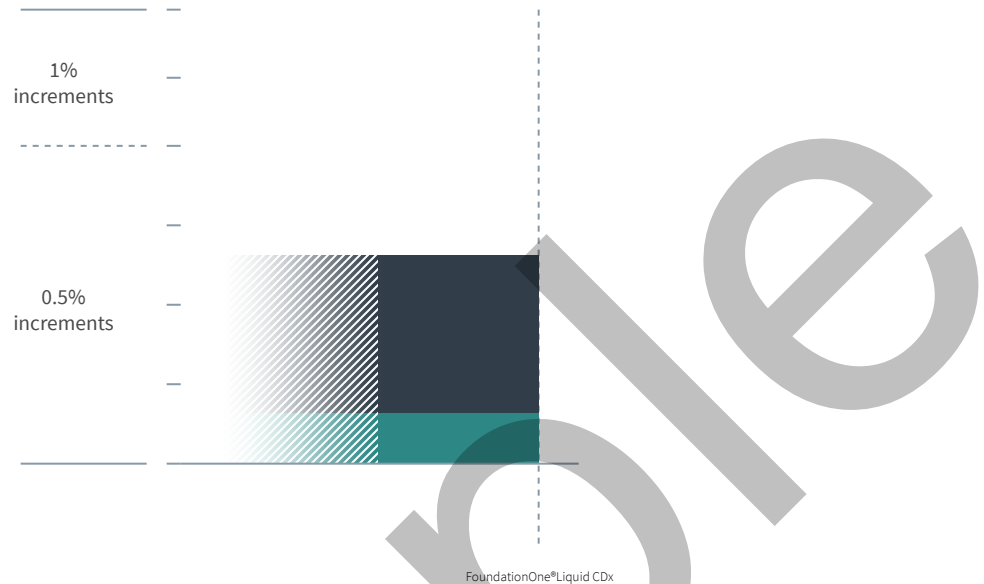
p. 6

**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.

ORDERED TEST #

Variant Allele Frequency  
Percentage (VAF%)



HISTORIC PATIENT FINDINGS		VAF%
<b>Blood Tumor Mutational Burden</b>		6 Muts/Mb
<b>Microsatellite status</b>		Cannot Be Determined
<b>Tumor Fraction</b>		Cannot Be Determined
<b>NF1</b>	● S892fs*10	0.99%
<b>ROS1</b>	CD74-ROS1 fusion	0.38%
<b>TP53</b>	● 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  $\geq 5\%$ , and bTMB is calculated based on variants with an allele frequency of  $\geq 0.5\%$ .

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

ORDERED TEST #

GENOMIC SIGNATURES

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<sup>1-2</sup> and anti-PD-1<sup>3</sup> 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<sup>1</sup>. In HNSCC, a Phase 3 trial showed

that bTMB  $\geq 16$  Muts/Mb (approximate equivalency  $\geq 8$  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<sup>4</sup>.

### FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)<sup>3</sup>. 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)<sup>5</sup>. 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<sup>6</sup>. However, no significant prognostic association of TMB and/or

PD-L1 status with survival has been reported in patients with lung SCC<sup>6-7</sup>.

### 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<sup>8-9</sup> and cigarette smoke in lung cancer<sup>10-11</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>12-13</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>14-18</sup>, and microsatellite instability (MSI)<sup>14,17-18</sup>. 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<sup>1-3</sup>.

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<sup>19-24</sup>.

### FREQUENCY & PROGNOSIS

Detectable 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)<sup>25</sup>. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer<sup>26</sup>, Ewing sarcoma and osteosarcoma<sup>27</sup>, prostate cancer<sup>22</sup>, breast cancer<sup>28</sup>, leiomyosarcoma<sup>29</sup>, esophageal cancer<sup>30</sup>, colorectal cancer<sup>31</sup>, and gastrointestinal cancer<sup>32</sup>.

### 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<sup>25,33-34</sup>. 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<sup>22,28,31</sup>, 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<sup>20,24,35</sup>. 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.

ORDERED TEST #

GENE ALTERATIONS

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<sup>36-37</sup> and neurofibromatosis-associated glioma or glioblastoma<sup>38-39</sup>, as well as extensive preclinical evidence in several tumor types<sup>40-45</sup>, 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<sup>46-48</sup> and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)<sup>49-50</sup>. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST<sup>51</sup>. 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<sup>52</sup>, 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<sup>53</sup>.

FREQUENCY & PROGNOSIS

In the TCGA datasets, NF1 mutation has been observed in 11% of lung adenocarcinoma cases<sup>54</sup> and 8% of lung squamous cell carcinoma cases<sup>55</sup>. 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<sup>56</sup>.

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway<sup>57</sup>. Neurofibromin acts as a tumor suppressor by repressing RAS signaling<sup>58</sup>. NF1 alterations that result in loss or disruption of the GAP-related domain<sup>59-62</sup>, as observed here, are predicted to be inactivating<sup>58,62-67</sup>. 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<sup>68-70</sup>. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000<sup>71-72</sup>, 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<sup>73</sup>, entrectinib<sup>74</sup>, ceritinib<sup>75</sup>, and lorlatinib<sup>76-77</sup> have shown significant clinical activity for patients with ROS1-rearranged NSCLC. Treatment with either brigatinib<sup>78</sup> or cabozantinib<sup>79-82</sup> 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)<sup>83</sup> and 81.8% (9/11)<sup>84</sup> for patients with TKI-naïve 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])<sup>83-84</sup>, and 1 study reported a shorter duration of response than in the first-line setting (10.2 months vs. not reached)<sup>84</sup>. 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-naïve patients<sup>85</sup>. 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<sup>86</sup>.

FREQUENCY & PROGNOSIS

ROS1 rearrangements or fusions have been reported in 1-2% of non-small cell lung carcinoma (NSCLC) tumors<sup>87-90</sup>, including in 1-3.4% of lung adenocarcinoma cases<sup>89,91-94</sup>. CD74-ROS1 fusions accounted for 23% (3/13) to 27% (5/18) of the ROS1 rearrangements identified in two studies of lung cancer<sup>88,92</sup>. Elevated ROS1 protein levels have been observed in 22% of NSCLC samples evaluated in one study<sup>95</sup>. 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<sup>90</sup>. Positive kinase fusion status (ALK, ROS1, or RET) was associated with improved prognosis in lung adenocarcinoma, independently of other

prognostic factors<sup>88</sup>, although never-smokers with surgically resected lung adenocarcinoma and ALK or ROS1 fusion had significantly shorter disease-free survival (hazard ratio, 2.11)<sup>94</sup>. 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<sup>93</sup>.

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<sup>96</sup>. ROS1 fusions involving the kinase domain of ROS1 (exons 36-42), as seen here, have been characterized as activating and oncogenic<sup>87-89,92,95-101</sup>. Patients with non-small cell lung cancer (NSCLC) and activating ROS1 fusions have experienced clinical benefit from crizotinib<sup>102-104</sup>.

ORDERED TEST #

GENE ALTERATIONS

GENE

TP53

ALTERATION

I332fs\*24

TRANSCRIPT ID

NM\_000546

CODING SEQUENCE EFFECT

955\_956insAGAAGAAACCACTGGATGGAGAATATTTACACC  
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<sup>115-118</sup>, or p53 gene therapy and immunotherapeutics such as SGT-53<sup>119-123</sup> and ALT-801<sup>124</sup>. 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<sup>125</sup>. 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<sup>126</sup>. 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<sup>127</sup>. 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<sup>128</sup>. 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<sup>129</sup>. 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<sup>130</sup>. 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<sup>123</sup>. 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<sup>131</sup>. 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<sup>132-133</sup>; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies<sup>134-135</sup>. 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)<sup>54-55,136-141</sup>, including 38-54% of lung adenocarcinomas and 47-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Sep 2020)<sup>54-55,142-143</sup>. 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<sup>144</sup>. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma<sup>99</sup>. 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<sup>145-150</sup>. CHIP is associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy<sup>145-146</sup>. Clinical management of patients with CHIP may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease<sup>151</sup>. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CHIP<sup>149,152-153</sup>. 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<sup>154</sup>. 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<sup>155-159</sup>. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers<sup>160-162</sup>, including sarcomas<sup>163-164</sup>. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000<sup>165</sup> to 1:20,000<sup>164</sup>. 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<sup>166</sup>. In the appropriate clinical context, germline testing of TP53 is recommended.



ORDERED TEST #

THERAPIES APPROVED IN THE EU

IN PATIENT'S TUMOR TYPE

## 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<sup>78,167</sup> and strong preclinical evidence<sup>168-169</sup>, ROS1 rearrangements may predict sensitivity to brigatinib.

### SUPPORTING DATA

Brigatinib has been studied primarily for the treatment of

ALK-rearranged NSCLC<sup>170-172</sup>. Brigatinib was associated with an ORR of 17% (3/18 patients) in other solid tumors with ALK/ROS1/EGFR alterations<sup>78</sup>. 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<sup>167</sup>. 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-naïve experienced a PR lasting >21 months<sup>78</sup>. A case study of 4 patients with ROS1-rearranged NSCLC who had progressed on crizotinib reported a 25% (1/4) ORR<sup>173</sup>.

## 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<sup>75,174</sup>, ROS1 rearrangements may predict sensitivity to ceritinib.

### SUPPORTING DATA

Ceritinib has been shown to confer clinical benefit in patients with ALK/ROS1-rearranged NSCLC<sup>75,175</sup>. 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-naïve patients<sup>75</sup>. The median OS among all patients was 24 months, and 5/8 (63%) patients with brain metastases experienced intracranial disease control<sup>75</sup>. 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<sup>174</sup>. In patients with ROS1-rearranged NSCLC that have progressed on crizotinib, the clinical evidence for ceritinib is limited and mixed<sup>75,176-177</sup>. Among the two patients previously treated with crizotinib included in a Phase 2 study of ceritinib, neither responded to treatment<sup>75</sup>; 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<sup>167,177</sup>.

## 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<sup>73,89-90,92,113-114,178-183</sup> and IMT<sup>100</sup>.

### SUPPORTING DATA

Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements<sup>184-188</sup>, ROS1 rearrangements<sup>90,113-114,189-190</sup>, an NTRK1 fusion<sup>191</sup>, or MET

activation<sup>192-208</sup>. 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<sup>209</sup>. 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)<sup>73</sup>. High ORR to crizotinib in ROS1-rearranged NSCLC is observed in other studies<sup>189-190</sup>. 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<sup>189</sup>. 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<sup>90,114</sup>.

ORDERED TEST #

THERAPIES APPROVED IN THE EU

IN PATIENT'S TUMOR TYPE

## 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<sup>74,210-212</sup> and clinical benefit in other solid tumor types<sup>213-216</sup>, ROS1 fusions may predict sensitivity to entrectinib.

#### SUPPORTING DATA

Combined analysis of Phase 1 and Phase 2 trials of entrectinib in ROS1-inhibitor-naïve 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<sup>217</sup>. 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)<sup>217</sup>. A real-world study in ROS1-rearranged NSCLC reported median PFS of 19.0 and 8.5 months to entrectinib and crizotinib, respectively<sup>210</sup>. 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<sup>74,210-213,218</sup>, and preclinical sensitivity has been observed in NTRK fusion-positive AML cell lines<sup>219</sup>. 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<sup>74</sup>.

## 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<sup>76-77,220-223</sup> and preclinical<sup>223-225</sup> 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<sup>76,226</sup>. 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<sup>76</sup>. In the follow-up Phase 2 trial, patients who were crizotinib-naïve 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-naïve and -treated patients achieving an IC-ORR of 64% (7/11; 5 CRs, 2 PRs) and 50% (12/24; 9 CRs, 3 PRs), respectively<sup>77</sup>. In case studies, a patient with metastatic NSCLC harboring an EZR-ROS1 fusion and S1986Y/F dual mutations responded to lorlatinib<sup>223</sup>, 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<sup>221</sup>.



ORDERED TEST #

THERAPIES APPROVED IN THE EU

IN PATIENT'S TUMOR TYPE

## 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<sup>36,39</sup> and strong preclinical evidence<sup>41-45</sup>, 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<sup>227</sup>. 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<sup>228</sup>. 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<sup>229-231</sup>. 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<sup>232-234</sup>. 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<sup>235</sup>. 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<sup>236-238</sup>. 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<sup>239</sup>. 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<sup>52</sup>, 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<sup>53</sup>.

ORDERED TEST #

THERAPIES APPROVED IN THE EU

IN OTHER TUMOR TYPE

## 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<sup>36,39</sup> and strong preclinical evidence<sup>40-45</sup>, 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<sup>174</sup>. 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<sup>240</sup>. 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)<sup>241-242</sup>. 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)<sup>243</sup>. Single-arm and retrospective studies have suggested intracranial activity of binimetinib alone or combined with encorafenib for NRAS- or BRAF-mutated metastatic melanoma<sup>244-245</sup>. 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<sup>246</sup>. 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<sup>247</sup>. Although single-agent binimetinib has had limited efficacy in biliary tract cancer<sup>248-249</sup>, 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)<sup>250</sup> or binimetinib combined with capecitabine in patients with progression on gemcitabine (ORR 21%, DCR 76%, PFS 4.1 months, OS 7.8 months)<sup>251</sup>. 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<sup>174,252</sup> or in combination with other therapies<sup>253-256</sup>.

## 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<sup>79-82,257</sup> and preclinical activity in wild-type and mutant ROS1-fusion cell lines<sup>79-80,168,258</sup>.

### 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<sup>257</sup>. Other case studies of patients with ROS1-rearranged NSCLC previously treated with at least 1 ROS1 TKI have reported 4 PRs<sup>79-82</sup>, 3 SDs (duration of 2.2-7.4 months)<sup>81</sup>, and 1 PD<sup>259</sup>. 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<sup>260</sup>. 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<sup>261</sup>. 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<sup>262</sup>.

ORDERED TEST #

THERAPIES APPROVED IN THE EU

IN OTHER TUMOR TYPE

## 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<sup>36,39</sup> and strong preclinical evidence<sup>41-45</sup>, 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<sup>263-264</sup>. Single-agent cobimetinib has shown clinical

activity in the context of histiocytosis (ORR of 64.3%, 9/14)<sup>265</sup>. 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)<sup>266</sup>. 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<sup>267</sup>. 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<sup>268-269</sup>. 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<sup>270</sup>.

**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.

ORDERED TEST #

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](https://clinicaltrials.gov). However, [clinicaltrials.gov](https://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

ORDERED TEST #

**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



ORDERED TEST #

CLINICAL TRIALS

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)

ORDERED TEST #

**CLINICAL TRIALS**
**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)

**NCT04310007**
**PHASE 2**

Testing the Addition of the Pill Chemotherapy, Cabozantinib, to the Standard Immune Therapy Nivolumab Compared to Standard Chemotherapy for Non-small Cell Lung Cancer

**TARGETS**

MET, RET, ROS1, VEGFRs, PD-1

**LOCATIONS:** New Hampshire, Massachusetts, New York, Pennsylvania, Michigan

**NCT02927340**
**PHASE 2**

A Study of Lorlatinib in Advanced ALK and ROS1 Rearranged Lung Cancer With CNS Metastasis in the Absence of Measurable Extracranial Lesions

**TARGETS**

ROS1, ALK

**LOCATIONS:** Massachusetts

**NCT01639508**
**PHASE 2**

Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity

**TARGETS**

MET, RET, ROS1, VEGFRs

**LOCATIONS:** New York, New Jersey

**NCT02693535**
**PHASE 2**

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

**TARGETS**

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

**LOCATIONS:** Pennsylvania, Virginia, Michigan, Illinois, Indiana, North Carolina, North Dakota

ORDERED TEST #

APPENDIX

Variants of Unknown Significance

**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

APPENDIX

Genes assayed in FoundationOne®Liquid CDx

ORDERED TEST #

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.

<b>ABL1</b> Exons 4-9	ACVR1B	<b>AKT1</b> Exon 3	AKT2	AKT3	<b>ALK</b> Exons 20-29, Introns 18, 19	ALOX12B	AMER1 (FAM123B)	<b>APC</b>
<b>AR</b>	<b>ARAF</b> Exons 4, 5, 7, 11, 13, 15, 16	ARFRP1	ARID1A	ASXL1	<b>ATM</b>	<b>ATR</b>	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BCR* Introns 8, 13, 14	<b>BRAF</b> Exons 11-18, Introns 7-10	<b>BRCA1</b> Introns 2, 7, 8, 12, 16, 19, 20	<b>BRCA2</b> Intron 2	BRD4	BRIP1	BTG1
BTG2	<b>BTK</b> Exons 2, 15	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8	CBFB	CBL
<b>CCND1</b>	CCND2	CCND3	CCNE1	CD22	CD70	CD74* Introns 6-8	CD79A	CD79B
<b>CD274</b> (PD-L1)	CDC73	<b>CDH1</b>	<b>CDK12</b>	<b>CDK4</b>	<b>CDK6</b>	CDK8	CDKN1A	CDKN1B
<b>CDKN2A</b>	CDKN2B	CDKN2C	CEBPA	CHEK1	<b>CHEK2</b>	CIC	CREBBP	<b>CRKL</b>
CSF1R	CSF3R	CTCF	CTNNA1	<b>CTNNB1</b> Exon 3	CUL3	CUL4A	CXCR4	CYP17A1
DAXX	DDR1	<b>DDR2</b> Exons 5, 17, 18	DIS3	DNMT3A	DOT1L	EED	<b>EGFR</b> Introns 7, 15, 24-27	EP300
EPHA3	EPHB1	EPHB4	<b>ERBB2</b>	<b>ERBB3</b> Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25	ERBB4	ERCC4	ERG	<b>ERRF1</b>
<b>ESR1</b> Exons 4-8	ETV4* Intron 8	ETV5* Introns 6, 7	<b>ETV6*</b> Introns 5, 6	EWSR1* Introns 7-13	<b>EZH2</b> Exons 4, 16, 17, 18	EZR* Introns 9-11	FAM46C	FANCA
FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14	FGF19
FGF23	FGF3	FGF4	FGF6	<b>FGFR1</b> Introns 1, 5, Intron 17	<b>FGFR2</b> Intron 1, Intron 17	<b>FGFR3</b> Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17	FGFR4	FH
FLCN	FLT1	<b>FLT3</b> Exons 14, 15, 20	<b>FOXL2</b>	FUBP1	GABRA6	GATA3	GATA4	GATA6
<b>GNA11</b> Exons 4, 5	GNA13	<b>GNAQ</b> Exons 4, 5	<b>GNAS</b> Exons 1, 8	GRM3	GSK3B	H3F3A	HDAC1	HGF
HNF1A	<b>HRAS</b> Exons 2, 3	HSD3B1	ID3	<b>IDH1</b> Exon 4	<b>IDH2</b> Exon 4	IGF1R	IKBKE	IKZF1
INPP4B	IRF2	IRF4	IRS2	JAK1	<b>JAK2</b> Exon 14	<b>JAK3</b> Exons 5, 11, 12, 13, 15, 16	JUN	KDM5A
KDM5C	KDM6A	KDR	KEAP1	KEL	<b>KIT</b> Exons 8, 9, 11, 12, 13, 17, Intron 16	KLHL6	KMT2A (MLL) Introns 6, 8-11, Intron 7	KMT2D (MLL2)
<b>KRAS</b>	LTK	LYN	MAF	<b>MAP2K1</b> (MEK1) Exons 2, 3	<b>MAP2K2</b> (MEK2) Exons 2-4, 6, 7	MAP2K4	MAP3K1	MAP3K13

APPENDIX

Genes assayed in FoundationOne®Liquid CDx

ORDERED TEST #

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	<b>MDM2</b>	MDM4	MED12	MEF2B	MEN1	MERTK	<b>MET</b>
MITF	MKNK1	MLH1	<b>MPL</b> Exon 10	MRE11A	MSH2 Intron 5	MSH3	MSH6	MST1R
MTAP	<b>MTOR</b> Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56	MUTYH	MYB* Intron 14	<b>MYC</b> Intron 1	MYCL (MYCL1)	<b>MYCN</b>	<b>MYD88</b> Exon 4	NBN
<b>NF1</b>	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2 Intron 26	NOTCH3	<b>NPM1</b> Exons 4-6, 8, 10
<b>NRAS</b> Exons 2, 3	NSD3 (WHSC1L1)	NTSC2	<b>NTRK1</b> Exons 14, 15, Introns 8-11	NTRK2 Intron 12	<b>NTRK3</b> Exons 16, 17	NUTM1* Intron 1	P2RY8	<b>PALB2</b>
PARK2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	<b>PDCD1LG2</b> (PD-L2)	<b>PDGFRA</b> Exons 12, 18, Introns 7, 9, 11
<b>PDGFRB</b> Exons 12-21, 23	PDK1	PIK3C2B	PIK3C2G	<b>PIK3CA</b> 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
<b>PTEN</b>	<b>PTPN11</b>	PTPRO	QKI	RAC1	RAD21	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	<b>RAF1</b> Exons 3, 4, 6, 7, 10, 14, 15, 17, Introns 4-8	RARA Intron 2	<b>RB1</b>	RBM10	REL	<b>RET</b> Introns 7, 8, Exons 11, 13-16, Introns 9-11
RICTOR	RNF43	<b>ROS1</b> 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
<b>SMO</b>	SNCAIP	SOCS1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2
STAT3	<b>STK11</b>	SUFU	SYK	TBX3	TEK	TERC* ncRNA	<b>TERT*</b> Promoter	TET2
TGFB2	TIPARP	TMPPRSS2* Introns 1-3	TNFAIP3	TNFRSF14	<b>TP53</b>	TSC1	TSC2	TYRO3
U2AF1	<b>VEGFA</b>	VHL	WHSC1	WT1	XPO1	XRCC2	ZNF217	ZNF703

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

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



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**APPENDIX**

**About FoundationOne® Liquid CDx**

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.



**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  $\geq 5\%$ , and bTMB is calculated based on variants with an allele frequency of  $\geq 0.5\%$ .
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](http://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

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APPENDIX

About FoundationOne®Liquid CDx

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

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