

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

<b>PATIENT</b>	<b>DISEASE</b> Lung adenocarcinoma	<b>PHYSICIAN</b>	<b>ORDERING PHYSICIAN</b> Yeh, Yi-Chen	<b>SPECIMEN</b>	<b>SPECIMEN ID</b> CHM 06/04/1953
	<b>NAME</b> Ma, Chun-Hua		<b>MEDICAL FACILITY</b> Taipei Veterans General Hospital		<b>SPECIMEN TYPE</b> Blood
	<b>DATE OF BIRTH</b> 04 June 1953		<b>ADDITIONAL RECIPIENT</b> None		<b>DATE OF COLLECTION</b> 31 May 2023
	<b>SEX</b> Female		<b>MEDICAL FACILITY ID</b> 205872		<b>SPECIMEN RECEIVED</b> 05 June 2023
	<b>MEDICAL RECORD #</b> 49073690		<b>PATHOLOGIST</b> Not Provided		

## Biomarker Findings

**Blood Tumor Mutational Burden** - 0 Muts/Mb  
**Microsatellite status** - MSI-High Not Detected  
**Tumor Fraction** - Elevated Tumor Fraction Not Detected

## Genomic Findings

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

**KRAS G12R**  
**STK11 Y60fs\*1**  
**CDKN2A/B p16INK4a D156fs\*37**  
**TP53 P190L**

## Report Highlights

- Evidence-matched clinical trial options based on this patient's genomic findings: (p. [12](#))
- Variants with prognostic implications for this tumor type that may impact treatment decisions: **KRAS G12R** (p. [7](#))

### BIOMARKER FINDINGS

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

**Microsatellite status** -  
 MSI-High Not Detected

**Tumor Fraction** -  
 Elevated Tumor Fraction Not Detected

### THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).

Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).

### GENOMIC FINDINGS

### VAF%

**KRAS** - G12R 0.53%

10 Trials see p. [12](#)

**STK11** - Y60fs\*1 0.62%

2 Trials see p. [14](#)

### THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)

None

### THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)

None

None

None

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**GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS**

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

**CDKN2A/B - p16INK4a D156fs\*37** ..... **p. 10**    **TP53 - P190L** ..... **p. 11**

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

Variant Allele Frequency is not applicable for copy number alterations.

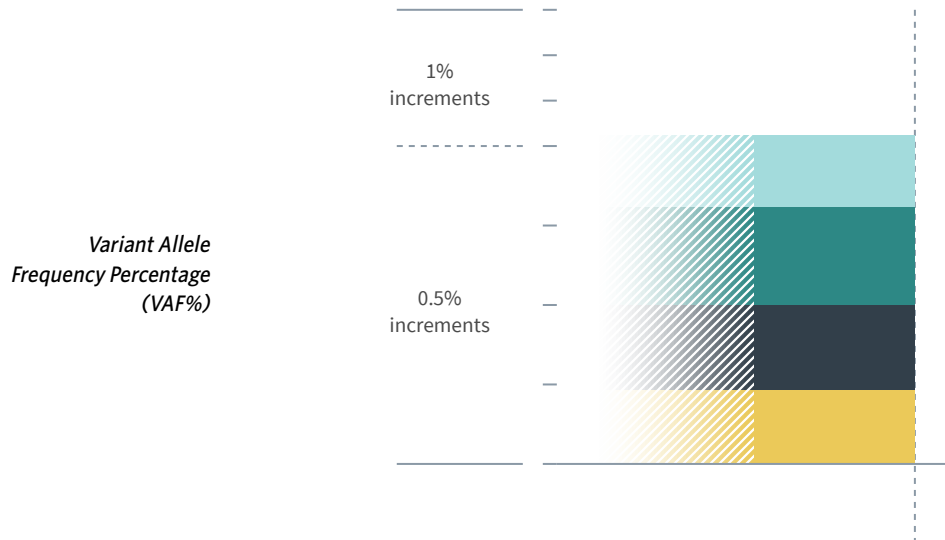
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FoundationOne®Liquid CDx  
12 Jun 2023

#### HISTORIC PATIENT FINDINGS

ORD-1644143-01  
VAF%

#### Blood Tumor Mutational Burden

0 Muts/Mb

#### Microsatellite status

MSI-High Not Detected

#### Tumor Fraction

Elevated Tumor Fraction Not Detected

<b>KRAS</b>	● G12R	0.53%
<b>STK11</b>	● Y60fs*1	0.62%
<b>CDKN2A/B</b>	● p16INK4a D156fs*37	0.47%
<b>TP53</b>	● P190L	0.63%

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

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. Variants reported for prior time points reflect reporting practices at the time of the historical test(s). Changes in variant reporting nomenclature, classification, or handling may result in the appearance of discrepancies across time points. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

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

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

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

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BIOMARKER FINDINGS

BIOMARKER

# Blood Tumor Mutational Burden

RESULT

0 Muts/Mb

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased blood tumor mutational burden (bTMB) may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1<sup>1-3</sup>, anti-PD-1<sup>3-4</sup>, anti-PD-1/CTLA4 therapies<sup>5-6</sup>, anti-PD-L1/CTLA4 therapies<sup>7-10</sup>. A Phase 2 multi-solid-tumor trial showed that bTMB  $\geq 16$  Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor<sup>5</sup>. In non-small cell lung cancer (NSCLC), multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single-agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 Muts/Mb-16 Muts/Mb<sup>1,8-10</sup>. In head and neck squamous cell carcinoma (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>11</sup>. In colorectal cancer (CRC), a Phase 2 study showed that bTMB  $\geq 28$  Muts/Mb (approximate equivalency  $\geq 14$  Muts/Mb as measured by this assay) was associated with improved OS from a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor<sup>7</sup>.

## FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)<sup>4</sup>. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic non-small cell lung cancer (NSCLC) reported that bTMB  $\geq 7$  Muts/Mb was associated with shorter PFS (2.8 vs. 4.2 months) and OS (7.4 vs. 11.9 months) compared with bTMB  $< 7$  Muts/Mb for patients treated with docetaxel<sup>12</sup>. In one study of advanced NSCLC in China, bTMB  $\geq 6$  Muts/Mb was associated with decreased PFS (10 vs. 18 months) and OS (11 vs. 25 months) compared with bTMB  $< 6$  Muts/Mb for patients treated with platinum-based chemotherapy<sup>13</sup>. A meta-analysis of 19 studies of immune checkpoint inhibitor-treated NSCLC (n = 2,315 patients) demonstrated that high TMB predicted a significantly longer OS than low TMB (HR = 0.70), and within the high TMB group, immunotherapy was associated with an improved PFS (HR = 0.62, P<0.001), OS (HR = 0.67, P<0.001) and a higher response rate (OR = 2.35, P<0.001) compared to chemotherapy<sup>14</sup>. In contrast, a large study of Chinese patients with untreated lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation

number (48.4 vs. 61.0 months)<sup>15</sup>. Another study of patients with NSCLC treated with EGFR inhibitors or platinum doublet chemotherapy found elevated TMB to be correlated with poorer prognosis, as well as finding lower TMB in combination with PD-L1 negative status to be significantly associated with longer median survival in patients with lung adenocarcinoma<sup>16</sup>. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC<sup>16-17</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>18-19</sup> and cigarette smoke in lung cancer<sup>20-21</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>22-23</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>24-28</sup>, and microsatellite instability (MSI)<sup>24,27-28</sup>. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents<sup>1-24</sup>. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

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**BIOMARKER FINDINGS**
**BIOMARKER**

# Tumor Fraction

**RESULT**

Elevated Tumor Fraction Not Detected

**POTENTIAL TREATMENT STRATEGIES**
**— Targeted Therapies —**

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not

be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management<sup>29-34</sup>.

**FREQUENCY & PROGNOSIS**

Detectable ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)<sup>35</sup>. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer<sup>36</sup>, Ewing sarcoma and osteosarcoma<sup>37</sup>, prostate cancer<sup>32</sup>, breast cancer<sup>38</sup>, leiomyosarcoma<sup>39</sup>, esophageal cancer<sup>40</sup>, colorectal

cancer<sup>41</sup>, and gastrointestinal cancer<sup>42</sup>.

**FINDING SUMMARY**

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content<sup>43</sup>, the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy<sup>44-45</sup>.

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GENOMIC FINDINGS

GENE

**KRAS**

ALTERATION

G12R

HGVS VARIANT

NM\_004985.3:c.34G>C (p.G12R)

VARIANT CHROMOSOMAL POSITION

chr12:25398285

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib<sup>46-51</sup>. In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NSCLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma<sup>52</sup>. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated LGSOC and 12% (2/17) for patients with KRAS-mutated NSCLC in a Phase 1 study<sup>53-54</sup>. Combination approaches of MEK inhibitors with chemotherapy have been investigated in KRAS-mutated NSCLC<sup>55-56</sup>; a Phase 3 study reported that addition of selumetinib to docetaxel did not improve PFS or OS for patients with KRAS-mutated NSCLC compared with docetaxel alone<sup>55</sup>. Multiple clinical studies have reported either low response rates or response rates similar to those of chemotherapy in patients with KRAS-mutated NSCLC receiving MEK inhibitors as a monotherapy<sup>57-59</sup>. Combinatorial approaches involving MEK inhibitors and other targeted therapies, including PI3K or EGFR inhibitors, have generally had limited clinical efficacy for patients with NSCLC and have been associated with high toxicity<sup>60-63</sup>. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors<sup>64-65</sup>. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations<sup>66</sup>. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer<sup>67</sup>. Preclinical

studies suggest that KRAS activating mutations may confer sensitivity to SOS1 inhibitors such as BI-3406, MRTX0902, BI-1701963, and BAY-293 as single agents<sup>68-73</sup> or in combination with covalent KRAS G12C inhibitors<sup>73</sup> and MEK inhibitors<sup>74-75</sup>. Immune checkpoint inhibitors (ICIs) have been associated with benefit for patients with KRAS-mutated NSCLC. Phase 3 studies of nivolumab<sup>76</sup> or atezolizumab<sup>77</sup> versus docetaxel in NSCLC post-platinum doublet therapy reported benefit for their respective KRAS-mutated subcohorts in addition to the cohorts overall; KRAS mutations in NSCLC are reported to correlate with PD-(L)1 status<sup>78</sup>. A retrospective analysis of pooled data from 12 clinical trials investigating ICI with or without chemotherapy for patients with NSCLC reported that patients with KRAS-mutated NSCLC, including KRAS G12C, benefited from first-line chemotherapy plus ICI similar to those with KRAS-wildtype NSCLC (median OS [mOS] of 22.4 vs. 18.7 months, ORR of 46% vs. 51%); the ICI plus chemotherapy combination exhibited improved outcomes compared with ICI alone or chemotherapy alone (mOS of 22.4 vs. 16.2 vs. 17.1 months)<sup>79</sup>. CDK4/6 inhibitors have been investigated in KRAS-mutated NSCLC; in a Phase 3 study of third-line platinum-refractory NSCLC, abemaciclib failed to improve mOS (7.4 months vs. 7.8 months, HR=0.97) relative to erlotinib in KRAS-mutated disease, despite increased ORR and PFS rates<sup>80</sup>. A Phase 1 combination trial of the CDK4/6 inhibitor palbociclib with MEK inhibitor mirdametinib included 17 patients with KRAS-mutated NSCLC and reported 1 PR, >50% SD, and 5 patients with PFS >6 months; clinical benefit was seen among patients with tumors harboring KRAS mutation alone or together with inactivation of TP53 or CDKN2A/B, but not among patients with tumors harboring KRAS mutation and STK11 inactivation<sup>81</sup>. Although some studies have suggested that KRAS mutation status may predict a lack of response to the EGFR inhibitors erlotinib and gefitinib for patients with lung cancer<sup>82-84</sup>, a retrospective study reported no statistically significant difference in response to EGFR tyrosine kinase inhibitors among KRAS-wildtype and KRAS-mutated disease independent from EGFR mutation status<sup>85</sup>. Co-occurring KRAS and STK11 alterations are associated with poorer response to ICIs for patients with NSCLC. Following anti-PD-1-based regimens, retrospective analyses have reported shorter OS for patients with KRAS- and STK11-mutated tumors than for those whose KRAS-mutated tumors were STK11-wildtype (6.4 vs. 16.1 months, HR=1.99), as well as markedly

fewer objective responses for patients with KRAS- and STK11-mutated versus KRAS- and TP53-mutated tumors in the CheckMate-057 (0% [0/6] vs. 57% [4/7])<sup>86</sup> and GEMINI (0% [0/6] vs. 53% [9/17])<sup>87</sup> studies. Another study observed that patients with NSCLC and KRAS-mutated tumors without STK11 alteration who were treated with second-line immunotherapy experienced similar median PFS (2.8 vs. 2.2 months, HR=1.64) and numerically longer median OS (7.7 vs. 3.5 months, HR=2.3; p=0.09) compared with patients harboring mutations in both KRAS and STK11<sup>88</sup>.

— Potential Resistance —

On the basis of limited clinical evidence, KEAP1 mutation may be associated with poor response to immunotherapy in NSCLC. Patients with NSCLC and concurrent mutation of STK11 and KEAP1 (n=39) who received treatment with a PD-L1 inhibitor experienced significantly shorter PFS (1.6 vs. 2.5 months; HR=1.5) and OS (4 vs. 11 months; HR=1.9) compared with patients with STK11- and KEAP1-wild-type tumors (n=210) despite significantly higher TMB in the dual mutated group (median 9.4 vs. 6.1 mut/Mb)<sup>89</sup>. However, exploratory analyses of patients with NSCLC treated in the first-line setting with pembrolizumab showed trends towards improved ORR and OS irrespective of STK11 or KEAP1 mutation status, although this was not demonstrated to be statistically significant<sup>90-91</sup>. Patients with NSCLC and STK11 or KEAP1 mutation treated with a PD-L1 inhibitor experienced significantly worse PFS (STK11 HR=2.04; KEAP1 HR=2.05) and OS (STK11 HR=2.09; KEAP1 HR=2.24) among patients with concurrent KRAS mutations but not patients with KRAS wildtype tumors<sup>92</sup>.

— Nontargeted Approaches —

KRAS mutation was associated with shorter PFS (7.0 vs. 8.6 months, p=0.026) and OS (14.2 vs. 21.6 months, p=0.019) with first-line treatment with bevacizumab plus chemotherapy in a retrospective study<sup>93</sup> and a lower major pathological response rate (0% [0/10] vs. 35.5% [11/31]) after neoadjuvant bevacizumab plus chemotherapy followed by adjuvant bevacizumab in a Phase 2 trial<sup>94</sup>, relative to those patients lacking KRAS mutation. However, addition of atezolizumab to first-line bevacizumab and chemotherapy improved PFS regardless of KRAS status in the Phase 3 IMPower150 study (HR=0.50 for KRAS mutant vs. 0.47 for KRAS wild-type vs. 0.67 for KRAS unknown)<sup>95</sup>.

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**GENOMIC FINDINGS**
**FREQUENCY & PROGNOSIS**

Studies have reported KRAS mutations in 10–38% of non-small cell lung cancers (NSCLC), including 27–37% of lung adenocarcinomas<sup>96–107</sup>, 10.5–33% of lung adenosquamous carcinomas<sup>108–110</sup>, 22% of lung large cell carcinoma without neuroendocrine features, and 6% of lung large cell neuroendocrine carcinomas<sup>111</sup>. KRAS mutation in lung adenocarcinoma has been correlated with disease progression, poorly differentiated tumors, and aggressive tumor behavior (NCCN NSCLC Guidelines, v2.2023)<sup>101,107,112</sup>. However, the

prognostic value of KRAS mutation in lung adenocarcinoma may differ among ethnic groups and may depend upon the specific allelic variant present<sup>113</sup>. In one study of 55 patients with lung adenocarcinoma, KRAS mutations, especially in combination with TP53 alterations, correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab, likely as a consequence of association with some immunogenic features such as tumor mutational burden<sup>114</sup>.

**FINDING SUMMARY**

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation<sup>47,115</sup>. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10\_A11insG, G10\_A11insAG (also reported as G10\_A11dup and G12\_G13insAG), A18D, L19F, D33E, G60\_A66dup/E62\_A66dup, E62K, E63K, R68S, K117R, and K117N have been characterized as activating and oncogenic<sup>47,116–138</sup>.

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



ORDERED TEST # ORD-1644143-01

GENOMIC FINDINGS

GENE

**STK11**

ALTERATION

Y60fs\*1

HGVS VARIANT

NM\_000455.4:c.180del (p.Y60\*)

VARIANT CHROMOSOMAL POSITION

chr19:1207091-1207092

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations<sup>139-142</sup>. Case studies have reported PRs for 2 patients with STK11-mutated pancreatic cancer following treatment with the mTOR inhibitor everolimus<sup>143</sup>, with 1 PR observed for a patient with Peutz-Jeghers syndrome for 9 months<sup>143</sup>. However, for patients with endometrial carcinoma, LKB1 (STK11) protein levels were not significantly correlated with response to everolimus<sup>144</sup>. Glutaminase inhibitors targeting GLS1 are under investigation for patients with STK11-mutated tumors<sup>145</sup>. Although 50% (1/2) of patients with STK11-mutated advanced NSCLC experienced an SD of 6 months with the GLS1 inhibitor IPN60090, 100% (2/2) of patients with ovarian cancers did not derive clinical benefit from this therapy<sup>145</sup>, and preclinical evidence for this targeted approach is conflicting<sup>146-149</sup>.

— Potential Resistance —

On the basis of limited clinical evidence, KEAP1 mutation may be associated with poor response to immunotherapy in NSCLC. Patients with NSCLC and concurrent mutation of STK11 and KEAP1 (n=39) who received treatment with a PD-L1

inhibitor experienced significantly shorter PFS (1.6 vs. 2.5 months; HR=1.5) and OS (4 vs. 11 months; HR=1.9) compared with patients with STK11- and KEAP1-wild-type tumors (n=210) despite significantly higher TMB in the dual mutated group (median 9.4 vs. 6.1 mut/Mb)<sup>89</sup>. However, exploratory analyses of patients with NSCLC treated in the first-line setting with pembrolizumab showed trends towards improved ORR and OS irrespective of STK11 or KEAP1 mutation status, although this was not demonstrated to be statistically significant<sup>90-91</sup>. Patients with NSCLC and STK11 or KEAP1 mutation treated with a PD-L1 inhibitor experienced significantly worse PFS (STK11 HR=2.04; KEAP1 HR=2.05) and OS (STK11 HR=2.09; KEAP1 HR=2.24) among patients with concurrent KRAS mutations but not patients with KRAS wildtype tumors<sup>92</sup>.

FREQUENCY & PROGNOSIS

Several clinical studies have found STK11 mutation to be common in non-small cell lung cancer (NSCLC) (15-35%), often co-occurring with activating KRAS mutations<sup>150-151</sup>, and are more prevalent in lung adenocarcinomas (13-34%) than in lung squamous cell carcinoma (2-19%)<sup>97,140,150-154</sup>. In the TCGA datasets, STK11 homozygous deletion was observed in 1% of lung adenocarcinoma cases<sup>98</sup> and was not observed in any of 178 lung squamous cell carcinoma cases<sup>154</sup>. The prognostic significance of STK11 mutations in patients with non-small cell lung cancer (NSCLC) is unclear. In an observational study of patients with advanced NSCLC, STK11 mutations were associated with significantly shorter OS (p=0.002) and reduced time to treatment failure (p=0.005)<sup>155</sup>; however, another retrospective study of patients enriched for advanced NSCLC reported no association between STK11 mutation status and survival<sup>156</sup>. For patients with Stage 1 or 2 NSCLC, 1 study reported a non-significant trend towards shorter survival for

patients with tumors harboring STK11 mutations (p=0.17)<sup>152</sup>. Other studies have reported reduced STK11 expression as a negative prognostic factor for patients with NSCLC<sup>157-158</sup>.

FINDING SUMMARY

The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels<sup>139</sup>. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis<sup>159-160</sup>. Alterations such as seen here may disrupt STK11 function or expression<sup>161-173</sup>.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the STK11 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Peutz-Jeghers syndrome (ClinVar, Apr 2023)<sup>174</sup>. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation<sup>175</sup>. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly<sup>175-177</sup>. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers<sup>175-177</sup>, and individuals with this syndrome have a 30-50% risk of developing breast cancer<sup>175,177</sup>. Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.

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ORDERED TEST # ORD-1644143-01

GENOMIC FINDINGS

GENE

**CDKN2A/B**

ALTERATION

p16INK4a D156fs\*37

HGVS VARIANT

NM\_000077.4:c.465del (p.D156fs\*37)

VARIANT CHROMOSOMAL POSITION

chr9:21968233-21968234

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib<sup>178-181</sup>. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib<sup>182</sup> and palbociclib treatment<sup>183-184</sup>. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents<sup>185-191</sup>; it is not known whether CDK4/6 inhibitors would be beneficial in this case.

FREQUENCY & PROGNOSIS

CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively<sup>98</sup>. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively<sup>154</sup>. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples<sup>154,192-197</sup>. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC<sup>194,198-200</sup>.

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b<sup>201-202</sup>. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway

and loss of cell cycle control<sup>193,203</sup>. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition<sup>204-205</sup>. One or more alterations observed here are predicted to result in p16INK4a loss of function<sup>206-227</sup>.

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer<sup>228</sup>. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma<sup>229-230</sup>. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases<sup>231-233</sup>. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors<sup>234-236</sup>. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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ORDERED TEST # ORD-1644143-01

GENOMIC FINDINGS

GENE  
**TP53**

ALTERATION  
P190L

HGVS VARIANT  
NM\_000546.4:c.569C>T (p.P190L)

VARIANT CHROMOSOMAL POSITION  
chr17:7578280

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib<sup>237-240</sup> or p53 gene therapy such as SGT53<sup>241-245</sup>. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype<sup>246</sup>. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer<sup>247</sup>. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer<sup>248</sup>. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone<sup>249</sup>. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel<sup>250</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% (5/7) response rate for patients with TP53

alterations<sup>251</sup>. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring<sup>252</sup>. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage<sup>245</sup>. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR<sup>253</sup>. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)<sup>254</sup>.

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>98,154,196,255-259</sup>, including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, 2023)<sup>97-98,154,260-263</sup>. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, 2023)<sup>262-263</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>114</sup>. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma<sup>264</sup>.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which

is encoded by the TP53 gene, is common in aggressive advanced cancers<sup>265</sup>. Alterations such as seen here may disrupt TP53 function or expression<sup>266-270</sup>.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Apr 2023)<sup>174</sup>. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers<sup>271-273</sup>, including sarcomas<sup>274-275</sup>. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000<sup>276</sup> to 1:20,000<sup>275</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>277</sup>. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion<sup>278-283</sup>. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy<sup>278-279</sup>. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease<sup>284</sup>. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH<sup>282,285-286</sup>. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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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

**KRAS**

## ALTERATION

G12R

## RATIONALE

KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS alterations are not predictive biomarkers for MEK inhibitor monotherapy in NSCLC and combinatorial approaches may yield improved efficacy. Limited clinical and preclinical studies

indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors. Preclinical evidence suggests that KRAS activating mutations may predict sensitivity to SOS1 inhibitors. Clinical evidence suggests that patients with KRAS-mutant NSCLC may be sensitive to the CDK4/6 inhibitor abemaciclib.

### NCT03337698

#### PHASE 1/2

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

#### TARGETS

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

**LOCATIONS:** Taipei City (Taiwan), Seoul (Korea, Republic of), Blacktown (Australia), Haifa (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Newcastle upon Tyne (United Kingdom), Dijon (France), London (United Kingdom), Sutton (United Kingdom)

### NCT04967079

#### PHASE 1

MEK Inhibitor Combined With Anlotinib in the Treatment of KRAS-mutated Advanced Non-small Cell Lung Cancer

#### TARGETS

MEK, FGFRs, KIT, VEGFRs

**LOCATIONS:** Shanghai (China)

### NCT04803318

#### PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

#### TARGETS

mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

**LOCATIONS:** Guangzhou (China)

### NCT04985604

#### PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

#### TARGETS

BRAF, MEK

**LOCATIONS:** Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

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**CLINICAL TRIALS**
**NCT03284502**
**PHASE 1**

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

**TARGETS**  
MEK, RAFs, NRAS

**LOCATIONS:** Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

**NCT04870034**
**PHASE NULL**

Binimetinib and Palbociclib Before Surgery for the Treatment of Operable KRAS-Positive Lung, Colorectal, or Pancreatic Cancer

**TARGETS**  
MEK, CDK4, CDK6

**LOCATIONS:** New York

**NCT05580770**
**PHASE 1/2**

Mirdametinib + BGB-3245 in Advanced Solid Tumors

**TARGETS**  
BRAF, MEK

**LOCATIONS:** Waratah (Australia), Melbourne (Australia), California, Ohio, Massachusetts, Texas, Connecticut, Florida

**NCT04551521**
**PHASE 2**

CRAFT: The NCT-PMO-1602 Phase II Trial

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

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

**NCT04892017**
**PHASE 1/2**

A Safety, Tolerability and PK Study of DCC-3116 in Patients With RAS or RAF Mutant Advanced or Metastatic Solid Tumors.

**TARGETS**  
ULK1, ULK2, MEK

**LOCATIONS:** Oregon, Massachusetts, New York, Texas, Pennsylvania

**NCT04720976**
**PHASE 1/2**

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

**TARGETS**  
MEK, SHP2, PD-1, EGFR, KRAS

**LOCATIONS:** Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

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**CLINICAL TRIALS**
**GENE**
**STK11**
**ALTERATION**
**Y60fs\*1**
**RATIONALE**

Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations.

**NCT03334617**
**PHASE 2**

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

**TARGETS**

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

**LOCATIONS:** Seoul (Korea, Republic of), Berlin (Germany), Wien (Austria), Großhansdorf (Germany), Salzburg (Austria), Innsbruck (Austria), Esslingen a.N. (Germany), Heidelberg (Germany), Edmonton (Canada), Paris (France)

**NCT04250545**
**PHASE 1**

Testing of the Anti Cancer Drugs CB-839 HCl (Telaglenastat) and MLN0128 (Sapanisertib) in Advanced Stage Non-small Cell Lung Cancer

**TARGETS**

mTORC1, mTORC2, GLS

**LOCATIONS:** California, New York

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**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.

**CD79B**

 NM\_000626.2: c.218A>C  
 (p.N73T)  
 chr17:62007646

**FANCA**

 NM\_000135.2: c.344G>A  
 (p.G115E)  
 chr16:89877419

**NOTCH3**

 NM\_000435.2: c.4348G>A  
 (p.A1450T)  
 chr19:15288391

**NTRK3**

 NM\_002530.2: c.61G>T  
 (p.V21F)  
 chr15:88799324

**PALB2**

 NM\_024675.3: c.3448C>T  
 (p.L1150F)  
 chr16:23614893

**PAX5**

 NM\_016734.1: c.203T>C  
 (p.I68T)  
 chr9:37020642

**PIK3CB**

 NM\_006219.1: c.2941C>T  
 (p.R981W)  
 chr3:138376533

**SNCAIP**

 NM\_005460.2: c.261G>T  
 (p.E87D)  
 chr5:121758693

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**APPENDIX**

Genes assayed in FoundationOne®Liquid CDx

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

<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 or WTX)	<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	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	EMSY (C11orf30)	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	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	GID4 (C17orf39)	<b>GNA11</b> Exons 4, 5
GNA13	<b>GNAQ</b> Exons 4, 5	<b>GNAS</b> Exons 1, 8	GRM3	GSK3B	H3-3A (H3F3A)	HDAC1	HGF	HNFI1A
<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>

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**APPENDIX**

Genes assayed in FoundationOne®Liquid CDx

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

LTK	LYN	MAF	<b>MAP2K1</b> (MEK1) Exons 2, 3	<b>MAP2K2</b> (MEK2) Exons 2-4, 6, 7	MAP2K4	MAP3K1	MAP3K13	MAPK1
MCL1	<b>MDM2</b>	MDM4	MED12	MEF2B	MEN1	MERTK	<b>MET</b>	MITF
MKNK1	MLH1	<b>MPL</b> Exon 10	MRE11 (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
NSD2 (WHSC1 or MMSET)	NSD3 (WHSC1L1)	NT5C2	<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>
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 9, 11
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	PRKN (PARK2)	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	RSP02* 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	TENT5C (FAM46C)	TERC* ncRNA	<b>TERT*</b> Promoter
TET2	TGFBR2	TIPARP	TMPRSS2* Introns 1-3	TNFAIP3	TNFRSF14	<b>TP53</b>	TSC1	TSC2
TYRO3	U2AF1	<b>VEGFA</b>	VHL	WT1	XPO1	XRCC2	ZNF217	ZNF703

**ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS**

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

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## 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, Ciplastraat 3, 2440 Geel, Belgium. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.



### ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

### INTENDED USE

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

### TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted

cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

### THE REPORT

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

### QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

### RANKING OF THERAPIES AND CLINICAL TRIALS

#### Ranking of Therapies in Summary Table

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

#### Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

### LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of  $\geq 5\%$ , 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 the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*,

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## APPENDIX

## About FoundationOne® Liquid CDx

*KMT2D (MLL2), MPL, MYD88, SF3B1, TET2, TP53, and U2AF1.*

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

## REPORT HIGHLIGHTS

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

## VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

## VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

## NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

## LEVEL OF EVIDENCE NOT PROVIDED

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

## NO GUARANTEE OF CLINICAL BENEFIT

This report makes no promises or guarantees that a particular drug will be effective in the treatment of

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

## NO GUARANTEE OF REIMBURSEMENT

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

## TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

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APPENDIX

About FoundationOne®Liquid CDx

**SELECT ABBREVIATIONS**

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

**REFERENCE SEQUENCE INFORMATION**

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

MR Suite Version (RG) 7.9.0

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**APPENDIX**
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