

**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> Esophagus squamous cell carcinoma (SCC)	<b>PHYSICIAN</b>	<b>ORDERING PHYSICIAN</b> Yeh, Yi-Chen	<b>SPECIMEN</b>	<b>SPECIMEN ID</b> C-MW 16/DEC/1957
	<b>NAME</b> Wang, Chu-Mao		<b>MEDICAL FACILITY</b> Taipei Veterans General Hospital		<b>SPECIMEN TYPE</b> Blood
	<b>DATE OF BIRTH</b> 16 December 1957		<b>ADDITIONAL RECIPIENT</b> None		<b>DATE OF COLLECTION</b> 23 December 2022
	<b>SEX</b> Male		<b>MEDICAL FACILITY ID</b> 205872		<b>SPECIMEN RECEIVED</b> 29 December 2022
	<b>MEDICAL RECORD #</b> 19787189		<b>PATHOLOGIST</b> Not Provided		

## Biomarker Findings

**Blood Tumor Mutational Burden** - 13 Muts/Mb  
**Microsatellite status** - MSI-High Not Detected  
**Tumor Fraction** - Elevated Tumor Fraction

## Genomic Findings

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

**CCND1** amplification  
**KRAS** amplification  
**BAP1** splice site 1117-6\_1143del33  
**CBL** splice site 1096-12\_1111del28  
**DNMT3A** E442\*, M439fs\*212  
**FGF19** amplification  
**FGF3** amplification  
**FGF4** amplification  
**MLL2** C735\*  
**TP53** H179Y, splice site 994-2A>T, splice site 376-1G>A

## Report Highlights

- Evidence-matched clinical trial options based on this patient's genomic findings: (p. [13](#))
- Variants that may represent clonal hematopoiesis and may originate from non-tumor sources: **DNMT3A** E442\*, **M439fs\*212** (p. [9](#)), **MLL2** C735\* (p. [11](#))

### BIOMARKER FINDINGS

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

10 Trials [see p. 13](#)

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

**Tumor Fraction** -  
Elevated Tumor Fraction

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

None

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

None

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. There is higher sensitivity for identifying genomic alterations and a lower risk of false negative results in specimens with elevated tumor fraction; the positive percent agreement observed between liquid and tissue for defined short variants is ≥ 90% (Li et al., 2021; AACR Abstract 2231) (see Biomarker Findings section).

### GENOMIC FINDINGS

### VAF%

**CCND1** - amplification -

6 Trials [see p. 15](#)

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

None

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

None

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GENOMIC FINDINGS	VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
<b>KRAS -</b> amplification	-	None	None
10 Trials see p. 17			

#### VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

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

**DNMT3A - E442\*, M439fs\*212** ..... p. 9 **MLL2 - C735\*** ..... p. 11

#### 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.

**BAP1 - splice site 1117-6\_1143del33** ..... p. 8 **FGF4 - amplification** ..... p. 10  
**CBL - splice site 1096-12\_1111del28** ..... p. 8 **MLL2 - C735\*** ..... p. 11  
**DNMT3A - E442\*, M439fs\*212** ..... p. 9 **TP53 - H179Y, splice site 994-2A>T, splice site**  
**FGF19 - amplification** ..... p. 9 **376-1G>A** ..... p. 12  
**FGF3 - amplification** ..... p. 10

**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, MUTHY, 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.

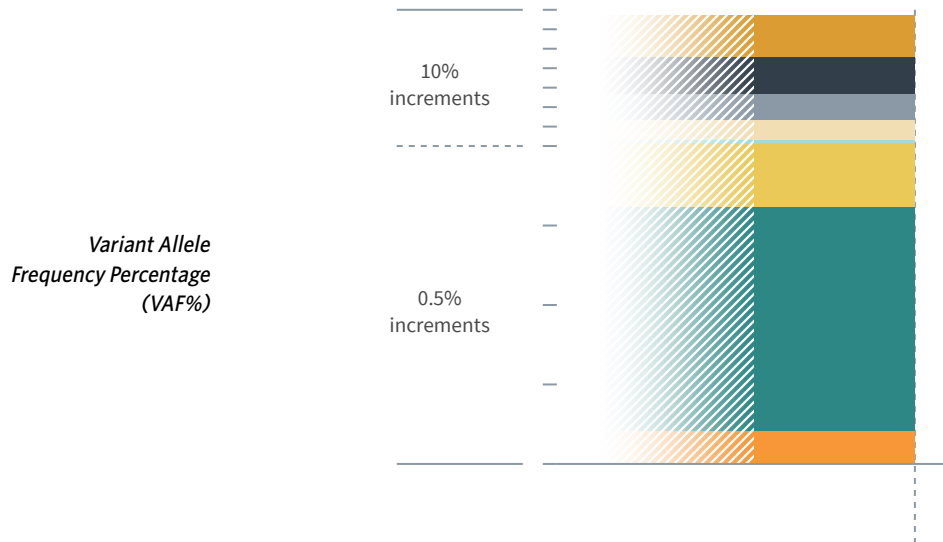
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FoundationOne®Liquid CDx  
07 Jan 2023

#### HISTORIC PATIENT FINDINGS

ORD-1533770-01  
VAF%

#### Blood Tumor Mutational Burden

13 Muts/Mb

#### Microsatellite status

MSI-High Not Detected

#### Tumor Fraction

33%

<b>CCND1</b>	amplification	Detected
<b>KRAS</b>	amplification	Detected
<b>BAP1</b>	● splice site 1117-6_1143del33	19.1%
<b>CBL</b>	● splice site 1096-12_1111del2 8	1.4%
<b>DNMT3A</b>	● M439fs*212	1.8%
	● E442*	1.9%
<b>FGF19</b>	amplification	Detected
<b>FGF3</b>	amplification	Detected
<b>FGF4</b>	amplification	Detected

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HISTORIC PATIENT FINDINGS		ORD-1533770-01 VAF%
<b>MLL2</b>	● C735*	12.9%
<b>TP53</b>	● splice site 376-1G>A	0.21%
	● splice site 994-2A>T	10.5%
	● H179Y	21.1%

**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. 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

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BIOMARKER FINDINGS

BIOMARKER

# Blood Tumor Mutational Burden

RESULT

13 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>.

### — Potential Resistance —

CCND1 amplification may predict worse outcomes on immune checkpoint inhibitors (anti-PD-1/PD-L1/CTLA-4) in solid tumors on the basis of 2 meta-analyses<sup>12-13</sup>; in these studies, CCND1 amplification was associated with significantly decreased response rate<sup>13</sup> and OS (HR=1.6-2.0)<sup>12-13</sup> across various tumor types and significantly shorter OS specifically in urothelial carcinoma (HR=2.2-3.6), melanoma (HR=1.6-2.5), and solid tumors harboring elevated TMB (HR=2.8)<sup>12-13</sup>.

## FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2022). For patients with squamous cell carcinoma (SCC) treated with PD-L1/PD-1 inhibitors, a Kaplan-Meier analysis showed a significant association for patients with high tumor mutational burden (TMB) with longer time to treatment failure (9.9 vs. 4.4 months)<sup>14</sup>. In the majority of cutaneous SCC cases, high mutational burden has been attributed to UV exposure rather than defective DNA mismatch repair or polymerase activity<sup>15-16</sup>, although one study reported a small number of cutaneous SCC cases (4/39) harboring a mutation signature similar to that of human papillomavirus-positive head and neck SCC<sup>16</sup>. In patients with non-small cell lung cancer (NSCLC), TMB is similar between cases with squamous and non-squamous histology<sup>17</sup>, and increased TMB is associated with higher tumor grade and poor

prognosis<sup>18</sup>, as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of high-TMB samples each) but not BRAF (10%) or KRAS (9.4%)<sup>17</sup>. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC<sup>18-19</sup>, several other large studies did find a strong prognostic association<sup>20-23</sup>. For patients with gastric cancer, increased TMB is reported to be associated with prolonged OS<sup>24-26</sup>. One study observed that the OS and disease-free survival (DFS) benefits of postoperative chemotherapy were more pronounced in patients with TMB-low gastric cancer (stage Ib/II) compared to those with TMB-high; however, patients with stage III gastric cancer benefitted regardless of TMB level<sup>27</sup>. In esophageal cancer, patients with TMB-high who had not received radiotherapy had significantly reduced OS (p=0.038) compared to those with TMB-low<sup>28</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>29-30</sup> and cigarette smoke in lung cancer<sup>31-32</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>33-34</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>35-39</sup>, and microsatellite instability (MSI)<sup>35,38-39</sup>. This sample harbors a bTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents<sup>1-24</sup>.

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**BIOMARKER FINDINGS**
**BIOMARKER**

# Tumor Fraction

**RESULT**

Elevated Tumor Fraction

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

Specimens with elevated tumor fraction have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. 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>40-45</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>46</sup>. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer<sup>47</sup>, Ewing sarcoma and osteosarcoma<sup>48</sup>, prostate cancer<sup>43</sup>, breast cancer<sup>49</sup>, leiomyosarcoma<sup>50</sup>, esophageal cancer<sup>51</sup>, colorectal cancer<sup>52</sup>, and gastrointestinal cancer<sup>53</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>54</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>55-56</sup>.

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GENOMIC FINDINGS

GENE  
**CCND1**

ALTERATION  
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib<sup>57-62</sup>, although as monotherapy these agents have shown limited activity in tumor types other than breast cancer<sup>61,63</sup>. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial<sup>64</sup>; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or

laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study<sup>64</sup>. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial<sup>65</sup>.

— Potential Resistance —

CCND1 amplification may predict worse outcomes on immune checkpoint inhibitors (anti-PD-1/PD-L1/CTLA-4) in solid tumors on the basis of 2 meta-analyses<sup>12-13</sup>; in these studies, CCND1 amplification was associated with significantly decreased response rate<sup>13</sup> and OS (HR=1.6-2.0)<sup>12-13</sup> across various tumor types and significantly shorter OS specifically in urothelial carcinoma (HR=2.2-3.6), melanoma (HR=1.6-2.5), and solid tumors harboring elevated TMB (HR=2.8)<sup>12-13</sup>.

— Nontargeted Approaches —

In addition, overexpression of cyclin D1 has been associated with a poor response to chemotherapy

and chemoradiotherapy in patients with ESCC<sup>66-67</sup>.

FREQUENCY & PROGNOSIS

Among gastroesophageal carcinomas, CCND1 amplification is most frequent in esophageal squamous cell carcinomas (ESCC; 22-70%)<sup>68-74</sup> and less frequent in esophageal adenocarcinomas (7-15%)<sup>74-76</sup> and gastric adenocarcinomas (6%)<sup>77</sup>. Expression of cyclin D1 has also been detected in 42-58% of ESCC samples<sup>71,78</sup>. CCND1 amplification and cyclin D1 overexpression have been correlated with tumor recurrence, reduced survival, and poor prognosis in patients with ESCC<sup>68,72,79-80</sup>.

FINDING SUMMARY

CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression<sup>81</sup> and may lead to excessive proliferation<sup>82-83</sup>.

GENE  
**KRAS**

ALTERATION  
amplification

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>84-89</sup>. Clinical evidence that KRAS amplification in the absence of a concurrent KRAS activating mutation is sensitive to MEK inhibitors is limited. A Phase 2 study of selumetinib plus

docetaxel in patients with gastric cancer reported 1 of 2 patients with KRAS amplification experienced a PR<sup>90</sup>. A patient with cervical cancer harboring both KRAS and PIK3CA amplification treated with the combination of trametinib and the AKT inhibitor GSK2141795 achieved a SD<sup>91</sup>.

FREQUENCY & PROGNOSIS

KRAS amplification has been reported in up to 27% of esophageal adenocarcinomas examined, compared with 17% of esophageal squamous cell carcinomas<sup>75,92-94</sup>. KRAS alterations, including mutations<sup>95</sup> and amplification<sup>94,96-97</sup> are associated with worse prognosis in patients with gastroesophageal cancer. One study reported that KRAS alteration did not significantly associate with OS in a cohort of patients with gastric,

esophageal, or gastroesophageal adenocarcinoma<sup>98</sup>. Published data investigating the prognostic implications of KRAS alterations in esophageal squamous cell carcinoma are limited (PubMed, Sep 2022).

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>85,99</sup>. In numerous cancer type-specific studies as well as a large-scale pan-cancer analysis, KRAS amplification was shown to correlate with increased expression<sup>100-103</sup>. Additionally, KRAS amplification correlated with sensitivity of cancer cell lines to KRAS knockdown, suggesting that amplified KRAS is an oncogenic driver<sup>103</sup>.

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GENOMIC FINDINGS

GENE

**BAP1**

ALTERATION

splice site 1117-6\_1143del33

TRANSCRIPT ID

NM\_004656.2

CODING SEQUENCE EFFECT

1117-6\_1143del33

VARIANT CHROMOSOMAL POSITION

chr3:52438575-52438608

inhibitors<sup>107-108</sup>. One preclinical study suggests that HDAC inhibitors may be beneficial in BAP1-mutated uveal melanoma; however, it is unclear if these inhibitors are effective in other BAP1-mutated cancers<sup>110</sup>.

**FREQUENCY & PROGNOSIS**

In esophageal squamous cell carcinomas, BAP1 mutation has been reported in 2% of cases<sup>111</sup> and one study reported deletion of the BAP1 locus in 52% (14/27) cases<sup>112</sup>. Published data investigating the prognostic implications of BAP1 alteration in esophageal carcinomas are limited (PubMed, Aug 2022).

to be a tumor suppressor<sup>113-114</sup>. Alterations such as seen here may disrupt BAP1 function or expression<sup>114-123</sup>.

**POTENTIAL GERMLINE IMPLICATIONS**

BAP1 germline inactivating alterations, including mutations and deletions, are associated with BAP1 tumor predisposition syndrome (BAP1-TPDS), an autosomal-dominant syndrome characterized by early onset of benign melanocytic skin tumors<sup>117,124-125</sup>. An estimated 2% of patients with BAP1-inactivated melanocytic tumors display germline BAP1 mutations<sup>126</sup>. Later in life, patients have an increased risk of cancers such as uveal melanoma, mesothelioma, clear cell renal cell carcinoma, basal cell carcinoma, and meningioma<sup>116-120,127</sup>. In small studies, the prevalence of pathogenic germline BAP1 mutation has been reported as 22% in familial uveal melanoma and 4.4% in mesothelioma<sup>128-129</sup>. In the appropriate clinical context, germline testing of BAP1 is recommended.

**POTENTIAL TREATMENT STRATEGIES**

— Targeted Therapies —

Clinical<sup>1104</sup> and preclinical<sup>1105</sup> evidence in the context of mesothelioma suggests that tumors with BAP1 inactivation may be sensitive to EZH2 inhibitors such as tazemetostat. Preclinical studies suggest that BAP1 is involved in the DNA damage response<sup>106-109</sup>, and BAP1 inactivation might be associated with sensitivity to PARP

**FINDING SUMMARY**

BAP1 (BRCA1 associated protein-1) encodes a ubiquitin hydrolase, a protein involved in regulating the availability of target proteins for the ubiquitin-proteasome protein degradation pathway; BAP1 is located on chromosome 3p21.3, in a region of frequent loss of heterozygosity (LOH) in breast and lung cancer, and has been postulated

GENE

**CBL**

ALTERATION

splice site 1096-12\_1111del28

TRANSCRIPT ID

NM\_005188.2

CODING SEQUENCE EFFECT

1096-12\_1111del28

VARIANT CHROMOSOMAL POSITION

chr11:119148862-119148890

which has shown activity in CBL-mutated advanced solid tumors<sup>136</sup>. Among 8 patients with CBL inactivating alterations in a Phase 1b trial, sitravatinib produced 2 PRs (25% ORR), with 1 NSCLC and 1 melanoma responding for over 4 months, and 4 SD outcomes, with 3 prolonged SDs seen in a patient with NSCLC, a patient with esophageal cancer, and a patient with a pancreatic neuroendocrine tumor<sup>136</sup>. CBL has been shown to downregulate EGFR<sup>137-141</sup> and FLT3<sup>142-144</sup>. Preclinical models of myeloid malignancies have demonstrated that CBL inactivation confers sensitivity to the FLT3-targeting therapies sunitinib<sup>142</sup>, midostaurin<sup>144</sup>, and quizartinib<sup>145</sup>, as well as to dasatinib<sup>146</sup>, although clinical evidence for this approach in solid tumors is lacking.

and in 0.9% of stomach adenocarcinomas (cBioPortal, Apr 2022)<sup>147-148</sup>. CBL protein expression was detected in 67% (82/122), and diffuse expression in 29% (25/122), of gastric carcinoma samples; the latter was associated with increased depth of invasion, lymph node metastasis, and tumor stage<sup>149</sup>.

**FINDING SUMMARY**

CBL encodes an E3 ubiquitin protein ligase that is involved in cell signaling and ubiquitination, targeting proteins such as EGFR, FGFR1, FGFR2, PDGFR-alpha, PDGFR-beta, FLT3, and SRC for degradation by the proteasome<sup>150-154</sup>. CBL alterations that result in loss or disruption of the tyrosine kinase binding domain, RING finger domain, and/or tail domain, as observed here, are predicted to be inactivating and to promote tumorigenesis<sup>155-172</sup>.

**POTENTIAL TREATMENT STRATEGIES**

— Targeted Therapies —

CBL inactivation may lead to the hyperactivation of various receptor tyrosine kinases (RTKs), including MET<sup>130</sup>, PDGFRA<sup>131</sup>, KIT<sup>132</sup>, VEGFR2<sup>133</sup>, and the TAM (TYRO3, AXL, MER) RTKs<sup>134</sup>. These RTKs are targets of the multikinase inhibitor sitravatinib<sup>135</sup>,

**FREQUENCY & PROGNOSIS**

CBL mutations have been reported in 3.5% of esophagogastric carcinomas, 3.2% of esophageal squamous cell carcinomas, 2.3% of esophagogastric,

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ORDERED TEST # ORD-1533770-01

GENOMIC FINDINGS

GENE

## DNMT3A

ALTERATION

E442\*, M439fs\*212

TRANSCRIPT ID

NM\_022552.3, NM\_022552.3

CODING SEQUENCE EFFECT

1324G>T, 1315delA

VARIANT CHROMOSOMAL POSITION

chr2:25469134, chr2:25469142-25469143

### POTENTIAL TREATMENT STRATEGIES

#### — Targeted Therapies —

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

### FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2022)<sup>147-148</sup>. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2022).

### FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation<sup>173-174</sup>. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor<sup>175-180</sup>. Alterations such as seen here may disrupt DNMT3A function or expression<sup>181-184</sup>.

### 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>185-190</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>185-186</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>191</sup>. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH<sup>189,192-193</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.

GENE

## FGF19

ALTERATION

amplification

### POTENTIAL TREATMENT STRATEGIES

#### — Targeted Therapies —

A Phase 1 study of the FGFR4 inhibitor fsgogatinib (BLU-554) for patients with advanced hepatocellular carcinoma (HCC) reported a 17% ORR (11/66, 1 CR, ongoing for >1.5 years) and 3.3-month PFS for FGF19 IHC-positive patients; patients with negative or unknown FGF19 IHC scores experienced poorer outcomes (0% ORR, 2.3-month PFS)<sup>194</sup>. A Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, demonstrated an ORR of 7.5% (4/53) and SD rate of 53% (28/53) for patients with HCC<sup>195</sup>. A Phase 1 study of the FGFR4 inhibitor H3B-6527 reported a 17% ORR (OS of 10.3 months, 46% clinical benefit rate) among

patients with HCC; enrollment of patients with intrahepatic cholangiocarcinoma (ICC) was suspended due to efficacy<sup>196</sup>. A retrospective analysis reported that 50% (2/4) of patients with HCC harboring FGF19 amplification experienced a CR to sorafenib<sup>197</sup>, though another retrospective study found patients with higher pretreatment serum levels of FGF19 experienced reduced benefit from sorafenib compared with those with lower serum FGF19 (PFS of 86 vs. 139 days, OS of 353 vs. 494 days); no difference was observed for lenvatinib<sup>198</sup>. A patient with head and neck squamous cell carcinoma (HNSCC) with 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) amplification experienced a CR lasting 9 months from a pan-FGFR inhibitor<sup>199</sup>.

### FREQUENCY & PROGNOSIS

For patients with solid tumors, FGF19 amplification has been reported most frequently in breast cancer (17%), head and neck cancer (12%), lung squamous cell carcinoma (SCC; 12%), and urothelial carcinoma cancer (11%)<sup>200-202</sup>. FGF19

mutations are rare in solid tumors<sup>200</sup>. FGF19 expression or amplification has been associated with poor prognosis in hepatocellular carcinoma (HCC)<sup>203-204</sup>, and in prostate cancer following radical prostatectomy<sup>205</sup>. Studies suggest FGF19 expression may also be a poor prognostic indicator in head and neck squamous cell carcinoma (HNSCC)<sup>206</sup> and lung SCC<sup>207</sup>.

### FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver<sup>208-209</sup>. FGF19 lies in a region of chromosome 11q13 that also contains FGF3, FGF4, and CCND1; this region is frequently amplified in a diverse range of malignancies<sup>210</sup>. Correlation between FGF19 amplification and protein expression has been reported in hepatocellular carcinoma (HCC)<sup>211</sup>, lung squamous cell carcinoma<sup>207,212</sup>, and head and neck squamous cell carcinoma (HNSCC)<sup>206</sup>, but was not observed in other cancers<sup>198,213</sup>.

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ORDERED TEST # ORD-1533770-01

GENOMIC FINDINGS

GENE  
**FGF3**

ALTERATION  
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in

a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR<sup>214</sup>.

FREQUENCY & PROGNOSIS

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell

cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies<sup>82</sup>.

FINDING SUMMARY

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures<sup>215</sup>.

GENE  
**FGF4**

ALTERATION  
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies<sup>216-217</sup> and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib ( $p=0.006$ )<sup>216</sup>. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR

inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR<sup>214</sup>.

FREQUENCY & PROGNOSIS

FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies<sup>82</sup> including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 24%), breast invasive carcinoma (14%), lung squamous cell carcinoma (13%), cholangiocarcinoma (11%), bladder urothelial carcinoma (10%), stomach adenocarcinoma (7%), skin melanoma (5%), and hepatocellular carcinoma

(HCC; 5%), however FGF4 amplification is rare in hematopoietic and lymphoid malignancies, reported in less than 1% of samples analyzed (cBioPortal, Jan 2023)<sup>147-148</sup>.

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth<sup>218</sup> and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development<sup>219</sup>. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers<sup>82,216,220-223</sup> and may confer sensitivity to the multi-kinase inhibitor sorafenib<sup>216</sup>.

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ORDERED TEST # ORD-1533770-01

**GENOMIC FINDINGS**
**GENE**
**MLL2**
**ALTERATION**  
C735\*

**TRANSCRIPT ID**  
NM\_003482.4

**CODING SEQUENCE EFFECT**  
2205C>A

**VARIANT CHROMOSOMAL POSITION**  
chr12:49445261

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

There are no targeted therapies available to address genomic alterations in MLL2.

**FREQUENCY & PROGNOSIS**

MLL2 alterations are observed in a number of solid tumor contexts<sup>200</sup>, and are especially prevalent in lung squamous cell carcinoma (SCC)<sup>201</sup> and small cell lung carcinoma (SCLC)<sup>224</sup>. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC<sup>225</sup>. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])<sup>226</sup>. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS<sup>227</sup>.

**FINDING SUMMARY**

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone

signaling<sup>228</sup>. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder<sup>229</sup>. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role<sup>230</sup>.

**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>185-190</sup>. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH<sup>189,192-193</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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ORDERED TEST # ORD-1533770-01

GENOMIC FINDINGS

GENE

TP53

ALTERATION

H179Y, splice site 994-2A>T, splice site 376-1G>A

TRANSCRIPT ID

NM\_000546.4, NM\_000546.4, NM\_000546.4

CODING SEQUENCE EFFECT

535C>T, 994-2A>T, 376-1G>A

VARIANT CHROMOSOMAL POSITION

chr17:7578395, chr17:7574035, chr17:7578555

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>231-234</sup> or p53 gene therapy such as SGT53<sup>235-239</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>240</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>241</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>242</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>243</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>244</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>245</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>246</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>239</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>247</sup>. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)<sup>248</sup>.

FREQUENCY & PROGNOSIS

TP53 mutations have been observed in 61-93% of esophageal squamous cell carcinoma samples<sup>249-251</sup>. While some studies have reported no association between TP53 mutation status and prognosis in patients with esophageal carcinoma or gastroesophageal junction adenocarcinoma<sup>252-253</sup> others have associated TP53 mutation and elevated p53 expression with poor prognosis for patients with esophageal squamous cell carcinoma<sup>254-255</sup> or stomach cancer<sup>256-258</sup>.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers<sup>259</sup>. Alterations such as

seen here may disrupt TP53 function or expression<sup>260-264</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, Sep 2022)<sup>265</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>266-268</sup>, including sarcomas<sup>269-270</sup>. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000<sup>271</sup> to 1:20,000<sup>270</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>272</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>185-190</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>185-186</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>191</sup>. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH<sup>189,192-193</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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**ORDERED TEST #** ORD-1533770-01

**CLINICAL TRIALS**

**IMPORTANT** Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or

research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or

in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see [clinicaltrials.gov](https://clinicaltrials.gov). However, [clinicaltrials.gov](https://clinicaltrials.gov) does not list all clinical trials that might be available.

**BIOMARKER**

## Blood Tumor Mutational Burden

**RESULT**

13 Muts/Mb

**RATIONALE**

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination

with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

**NCT04237649**
**PHASE NULL**

KAZ954 Alone and With PDR001, NZV930 and NIR178 in Advanced Solid Tumors

**TARGETS**

ADORA2A, CD73, PD-1

**LOCATIONS:** Taipei (Taiwan), Shatin, New Territories (Hong Kong), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Toronto (Canada), Missouri

**NCT04550260**
**PHASE 3**

Study of Durvalumab Versus Placebo in Combination With Definitive Chemoradiation Therapy in Patient With ESCC

**TARGETS**

PD-L1

**LOCATIONS:** Taipei (Taiwan), Tao-Yuan (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Quanzhou (China), Jieyang (China), Hangzhou (China)

**NCT04543617**
**PHASE 3**

A Study of Atezolizumab With or Without Tiragolumab in Participants With Unresectable Esophageal Squamous Cell Carcinoma Whose Cancers Have Not Progressed Following Definitive Concurrent Chemoradiotherapy

**TARGETS**

PD-L1, TIGIT

**LOCATIONS:** Zhongzheng Dist. (Taiwan), Taichung (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaoisung (Taiwan), Xiamen (China), Lishui City (China), Jieyang City (China), Zhejiang (China), Shanghai City (China)

**NCT04210115**
**PHASE 3**

Study of Pembrolizumab (MK-3475) Versus Placebo in Participants With Esophageal Carcinoma Who Are Receiving Chemotherapy and Radiation Therapy (MK-3475-975/KEYNOTE-975)

**TARGETS**

PD-1

**LOCATIONS:** Taipei (Taiwan), Taichung (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Xiamen (China), Hangzhou (China), Shanghai (China), Shanghai (China), Nanchang (China)

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**CLINICAL TRIALS**
**NCT04949256**
**PHASE 3**

Efficacy and Safety of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Plus Chemotherapy in Participants With Metastatic Esophageal Carcinoma (MK-7902-014/E7080-G000-320/LEAP-014)

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

**LOCATIONS:** Taipei (Taiwan), Kaohsiung (Taiwan), Fuzhou (China), Tainan (Taiwan), Xiamen (China), Hangzhou (China), Wuxi (China), Kowloon (Hong Kong), Hong Kong (Hong Kong), Hefei (China)

**NCT05166577**
**PHASE 1/2**

Nanatinostat Plus Valganciclovir in Patients With Advanced EBV+ Solid Tumors, and in Combination With Pembrolizumab in EBV+ RM-NPC

**TARGETS**  
HDAC, PD-1

**LOCATIONS:** Taipei City (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan), Sha Tin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Kuching (Malaysia), Kuala Lumpur (Malaysia), Singapore (Singapore), Blacktown (Australia)

**NCT04785820**
**PHASE 2**

A Study of RO7121661 and RO7247669 Compared With Nivolumab in Participants With Advanced or Metastatic Squamous Cell Carcinoma of the Esophagus

**TARGETS**  
PD-1, TIM-3, LAG-3

**LOCATIONS:** Zhongzheng Dist. (Taiwan), Jeollanam-do (Korea, Republic of), Seoul (Korea, Republic of), Bangkok (Thailand), Songkhla (Thailand), Singapore (Singapore), Van (Turkey), Moskva (Russian Federation), Moscow (Russian Federation), Erzurum (Turkey)

**NCT05007106**
**PHASE 2**

MK-7684A With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors (MK-7684A-005)

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

**LOCATIONS:** Taoyuan (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Seoul (Korea, Republic of), Osaka (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Alaska, Adana (Turkey)

**NCT03674567**
**PHASE 1/2**

Dose Escalation and Expansion Study of FLX475 Monotherapy and in Combination With Pembrolizumab

**TARGETS**  
PD-1, CCR4

**LOCATIONS:** Taipei (Taiwan), Tainan (Taiwan), Busan (Korea, Republic of), Shatin (Hong Kong), High West (Hong Kong), Chungbuk (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia)

**NCT04152018**
**PHASE 1**

Study of PF-06940434 in Patients With Advanced or Metastatic Solid Tumors.

**TARGETS**  
PD-1

**LOCATIONS:** Taipei (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Liverpool (Australia), Wollongong (Australia), Poprad (Slovakia), Bratislava (Slovakia), Washington, California, Arizona

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**ORDERED TEST #** ORD-1533770-01

**CLINICAL TRIALS**
**GENE**  
**CCND1**
**ALTERATION**  
amplification

**RATIONALE**  
CCND1 amplification or overexpression may activate CDK4/6 and may predict sensitivity to

single-agent CDK4/6 inhibitors.

**NCT04000529**
**PHASE 1**

Phase Ib Study of TNO155 in Combination With Spartalizumab or Ribociclib in Selected Malignancies

**TARGETS**  
PD-1, SHP2, CDK6, CDK4

**LOCATIONS:** Shanghai (China), Hong Kong (Hong Kong), Chengdu (China), Chuo ku (Japan), Singapore (Singapore), Westmead (Australia), Bruxelles (Belgium), Barcelona (Spain), Massachusetts

**NCT04282031**
**PHASE 1/2**

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

**TARGETS**  
CDK6, CDK4, ER, Aromatase

**LOCATIONS:** Shanghai (China)

**NCT04801966**
**PHASE NULL**

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

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

**LOCATIONS:** Melbourne (Australia)

**NCT03297606**
**PHASE 2**

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

**NCT05252416**
**PHASE 1/2**

(VELA) Study of BLU-222 in Advanced Solid Tumors

**TARGETS**  
ER, CDK4, CDK6, CDK2

**LOCATIONS:** Massachusetts, New York, Virginia, Texas, Florida

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ORDERED TEST # ORD-1533770-01

CLINICAL TRIALS

## NCT02896335

### PHASE 2

Palbociclib In Progressive Brain Metastases

**TARGETS**  
CDK4, CDK6

**LOCATIONS:** Massachusetts

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**CLINICAL TRIALS**
**GENE**  
**KRAS**
**ALTERATION**  
amplification

**RATIONALE**  
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors.

**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

**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)

**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)

**NCT04801966**
**PHASE NULL**

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

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

**LOCATIONS:** Melbourne (Australia)

**NCT04551521**
**PHASE 2**

CRAFT: The NCT-PMO-1602 Phase II Trial

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

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

**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**  
RAF, EGFR, MEK

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

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**CLINICAL TRIALS**
**NCT05159245**
**PHASE 2**

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

**TARGETS**

BRAf, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

**LOCATIONS:** Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

**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

**NCT04965818**
**PHASE 1/2**

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

**TARGETS**

MEK, FGFRs

**LOCATIONS:** California, Indiana, Texas

**NCT05340621**
**PHASE 1/2**

OKI-179 Plus Binimetinib in Patients With Advanced Solid Tumors in the RAS Pathway (Phase 1b) and NRAS-mutated Melanoma (Phase 2)

**TARGETS**

HDACs, MEK

**LOCATIONS:** Arizona, Illinois, Massachusetts, Texas, Georgia

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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.

**ARID1A**  
V1736M

**C11ORF30 (EMSY)**  
V739A

**CARD11**  
V197fs\*1

**FANCA**  
D694N, E369K and E484K

**FGF19**  
S50F

**FGFR1**  
A435V

**HSD3B1**  
L56Q

**JAK2**  
H1077R

**KDM5C**  
R332P

**LTK**  
R682Q

**MLL2**  
P777T

**NF1**  
H2479R

**PBRM1**  
I1573T

**PDGFRA**  
E485Q

**ROS1**  
V665L

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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>BTB</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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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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ORDERED TEST # ORD-1533770-01

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. 2022. 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) 7.4.0

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