

**ABOUT THE TEST** FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT	DISEASE	Colon adenocarcinoma (CRC)	PHYSICIAN	ORDERING PHYSICIAN	Yeh, Yi-Chen	SPECIMEN	SPECIMEN SITE	Colon
	NAME	Huang, Kuo Fu		MEDICAL FACILITY	Taipei Veterans General Hospital		SPECIMEN ID	S111-43820D (PF23066)
	DATE OF BIRTH	04 February 1965		ADDITIONAL RECIPIENT	None		SPECIMEN TYPE	Slide Deck
	SEX	Male		MEDICAL FACILITY ID	205872		DATE OF COLLECTION	25 October 2022
	MEDICAL RECORD #	35631153		PATHOLOGIST	Not Provided		SPECIMEN RECEIVED	26 May 2023

## Biomarker Findings

**Microsatellite status** - MS-Stable  
**Tumor Mutational Burden** - 4 Muts/Mb

## Genomic Findings

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

**KRAS** G12D  
**NRAS** wildtype  
**APC** Q1291\*  
**ARAF** amplification - equivocal†  
**CCND2** amplification  
**FGF23** amplification  
**FGF6** amplification  
**SMAD4** loss

3 Disease relevant genes with no reportable alterations: **BRAF**, **ERBB2**, **NRAS**

† See About the Test in appendix for details.

## Report Highlights

- Targeted therapies with **potential resistance** based on this patient's genomic findings: **Cetuximab** (p. 9), **Panitumumab** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

### BIOMARKER FINDINGS

**Microsatellite status** - MS-Stable

**Tumor Mutational Burden** - 4 Muts/Mb

### GENOMIC FINDINGS

**KRAS** - G12D

10 Trials see p. 16

**NRAS** - wildtype

0 Trials

**APC** - Q1291\*

3 Trials see p. 11

### THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

No therapies or clinical trials. See Biomarker Findings section

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
<b>Cetuximab</b>	✗	none
<b>Panitumumab</b>	✗	
<b>Cetuximab</b>	✗	none
<b>Panitumumab</b>	✗	
none		none

✗ Extensive evidence showing variant(s) in this sample may confer resistance to this therapy


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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
<b>ARAF</b> - amplification - equivocal	none	none
10 Trials see p. 12		
<b>CCND2</b> - amplification	none	none
8 Trials see p. 14		

 Extensive evidence showing variant(s) in this sample may confer resistance to this therapy

#### 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.

**FGF23** - amplification ..... p. 7    **SMAD4** - loss ..... p. 8  
**FGF6** - amplification ..... p. 7

**NOTE** Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents 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 exhaustive. Neither the therapeutic agents 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.

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## BIOMARKER FINDINGS

## BIOMARKER

## Microsatellite status

## RESULT

MS-Stable

### POTENTIAL TREATMENT STRATEGIES

#### — Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors<sup>1-3</sup>, including approved therapies nivolumab and pembrolizumab<sup>4</sup>. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%,  $p=0.001$ )<sup>5</sup>. For patients with chemotherapy-refractory microsatellite-stable (MSS) metastatic colorectal cancer (CRC), a Phase 3 trial reported no OS advantage from the combination of the PD-L1 inhibitor atezolizumab plus cobimetinib relative to regorafenib (8.9 vs. 8.5 months, HR=1.00);

atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)<sup>6</sup>. For patients with MSS CRC, a Phase 2 study combining ipilimumab and nivolumab reported an overall DCR of 25% (10/40)<sup>7</sup>. Two Phase 1 studies for patients with MSS CRC treated with regorafenib and nivolumab reported PFSs of 7.9 months<sup>8</sup> and 5.7 months<sup>9</sup>, and a patient with MSS CRC refractory to chemotherapy treated with the PD-1 inhibitor sintilimab and regorafenib reported a CR<sup>10</sup>.

#### — Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX<sup>11-12</sup> and FOLFIRI<sup>13-14</sup>. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy<sup>15-16</sup> but less likely to benefit from irinotecan chemotherapy<sup>17</sup>.

### FREQUENCY & PROGNOSIS

MSS colorectal cancers (CRCs) make up 70-85% of CRC cases<sup>3,18-22</sup>. MSS colorectal cancers are

molecularly heterogeneous, driven by diverse mechanisms such as extensive DNA methylation, oncogenic mutations in KRAS or BRAF, or chromosomal instability<sup>22</sup>. Multiple studies have shown that MSS CRCs have a worse prognosis than MSI-high tumors<sup>18,23-29</sup>.

### FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor<sup>20</sup>. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2<sup>20,30-31</sup>. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers<sup>19,32-33</sup>. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins<sup>19-20,31,33</sup>.

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## BIOMARKER FINDINGS

## BIOMARKER

# Tumor Mutational Burden

## RESULT

4 Muts/Mb

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1<sup>34-36</sup>, anti-PD-1 therapies<sup>34-37</sup>, and combination nivolumab and ipilimumab<sup>38-43</sup>. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors<sup>34-37,44-48</sup>. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB  $\geq 10$  Muts/Mb (as measured by this assay) compared with those with TMB  $< 10$  Muts/Mb in a large cohort that included multiple tumor types<sup>44</sup>; similar findings were observed in the KEYNOTE 028 and 012 trials<sup>37</sup>. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores  $\geq 10$  Muts/Mb were associated with prolonged time to treatment failure compared with scores  $< 10$  Muts/Mb (HR=0.68)<sup>48</sup>. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB  $\geq 10$  Muts/Mb independent of blood TMB at any cutpoint in matched samples<sup>49</sup>. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR

was seen in patients with TMB  $\geq 16$  Muts/Mb than those with TMB  $\geq 10$  and  $< 16$  Muts/Mb<sup>47</sup>. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as  $\geq 16-20$  Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy<sup>50</sup> or those with lower TMB treated with PD-1 or PD-L1-targeting agents<sup>35</sup>. In CRC specifically, a retrospective analysis of immune checkpoint inhibitor efficacy reported significantly improved OS for patients with tumors harboring TMB  $\geq 9.8$  Muts/MB compared with those with tumors with TMB  $< 9.8$  Muts/Mb (~equivalency  $< 12$  Muts/Mb as measured by this assay)<sup>34</sup>. Another retrospective study reported that a TMB  $\geq 12$  Muts/Mb cutoff identifies  $> 99\%$  of MSI-High CRC cases but only 3% of MSS cases, indicating the utility of this cutoff for identification of patients with CRC likely to benefit from treatment with immune checkpoint inhibitors<sup>51</sup>.

## FREQUENCY & PROGNOSIS

Elevated tumor mutational burden (TMB) has been reported in 8-25% of colorectal cancer (CRC) samples<sup>21,52-53</sup>. Multiple studies have reported that up to 90% of hypermutated CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)<sup>21,52</sup>. Increased TMB is significantly associated with MSI-H and MMR-D, with studies reporting that 100% of MSI-H CRCs harbor elevated TMB and conversely that 100% of tumors with low TMB harbor intact MMR<sup>52</sup>. A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which leads to an "ultramutated" phenotype with especially high TMB<sup>21,52</sup>. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB<sup>21,52</sup>, whereas TMB-low tumors more frequently harbor mutations in TP53 and APC<sup>21</sup>. The prognostic value of tumor mutational burden (TMB) in colorectal cancer (CRC) is context- and therapy-dependent. A

study of tissue TMB (tTMB) in 145 CRC samples showed longer OS in TMB-high samples compared with TMB-low ones<sup>54</sup>. Similarly, for patients with metastatic CRC treated with first-line chemotherapy combined with bevacizumab or cetuximab, high tissue TMB (tTMB-H) was associated with longer OS<sup>55</sup>. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival<sup>56</sup>. However, for patients with EGFR/BRAF-inhibitor-treated, BRAF-mutated microsatellite stable (MSS) metastatic CRC, intermediate tTMB was associated with significantly poorer PFS and OS compared with TMB-low status; patients with primary resistance to EGFR/BRAF blockage had higher TMB than those sensitive to these therapies<sup>57</sup>. In a study for 61 patients with metastatic, MSS CRC treated with best standard of care, plasma TMB scores  $\geq 28$  Muts/Mb (approximately 14 Muts/Mb as measured by this assay) were associated with reduced OS compared with plasma TMB scores  $< 28$  Muts/Mb (3.0 vs. 5.3 months, HR=0.76,  $p=0.007$ ), whereas tTMB was not found to be prognostic in this population<sup>58</sup>.

## FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma<sup>59-60</sup> and cigarette smoke in lung cancer<sup>61-62</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>63-64</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>21,65-68</sup>, and microsatellite instability (MSI)<sup>21,65,68</sup>. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents<sup>34,44,51</sup>.

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GENOMIC FINDINGS

GENE

**KRAS**

ALTERATION

G12D

HGVS VARIANT

NM\_004985.3:c.35G>A (p.G12D)

VARIANT CHROMOSOMAL POSITION

chr12:25398284

VARIANT ALLELE FREQUENCY (% VAF)

19.6%

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>69-74</sup>. However, multiple clinical trials have reported lack of efficacy of trametinib and other MEK inhibitors when used as monotherapy for treatment of patients with KRAS-mutant CRC<sup>75-79</sup>. Both clinical<sup>80-81</sup> and preclinical<sup>82-83</sup> studies suggest that combinatorial approaches including MEK inhibitors are likely to be more effective for the treatment of CRC, including strategies such as combination of MEK inhibitors with PI3K inhibitors<sup>81</sup>, RAF inhibitors<sup>82</sup>, pan-ERBB inhibitors<sup>83</sup>, or chemotherapeutic agents<sup>80</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>84</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>85-86</sup>. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors<sup>87-88</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>89</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>90</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>91-96</sup> or in combination with covalent KRAS G12C inhibitors<sup>96</sup> and MEK inhibitors<sup>97-98</sup>. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors<sup>99</sup>. A Phase 1b/2 study of PLK1 inhibitor onvansertib in combination with FOLFIRI and bevacizumab for patients with KRAS-mutated metastatic CRC previously treated with chemotherapy reported an 87.5% (7/8; 3 PR, 4 SD) clinical benefit rate, with 1 patient going on to successful curative surgery<sup>100</sup>. Preclinical and clinical data suggest that KRAS G12D mutations may predict clinical benefit from KRAS G12D-targeted, T-cell-receptor-based adoptive cell therapy<sup>101-103</sup>. Case studies of KRAS G12D-targeted, T-cell-receptor-based adoptive cell therapy have reported PRs for pretreated patients with metastatic pancreatic adenocarcinoma<sup>101</sup> or colorectal cancer (CRC)<sup>102</sup>. Preclinical data suggests

that KRAS G12D mutations may predict sensitivity to KRAS G12D small-molecule inhibitors, such as MRTX1133<sup>104-108</sup> and RMC9805<sup>109</sup>.

— Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab<sup>110-113</sup> or panitumumab<sup>114-116</sup> for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v3.2022).

FREQUENCY & PROGNOSIS

Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)<sup>117-125</sup>. Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC<sup>119-122,126-127</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>70,128</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>70,129-151</sup>.

GENE

**NRAS**

ALTERATION

wildtype

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-

targeting antibodies cetuximab<sup>110-113</sup> or panitumumab<sup>114-116</sup> for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Colon Cancer Guidelines, v3.2022, Rectal Cancer Guidelines, v4.2022).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations<sup>21,125,152-157</sup>. NRAS wild-type status has been reported to be associated with decreased

frequency of metastasis<sup>125</sup> and longer survival<sup>157-158</sup> of patients with CRC.

FINDING SUMMARY

NRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways<sup>70</sup>. No alterations in NRAS were identified in this case.

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**GENOMIC FINDINGS**
**GENE**

# APC

**ALTERATION**

Q1291\*

**HGVS VARIANT**

NM\_000038.4:c.3871C&gt;T (p.Q1291\*)

**VARIANT CHROMOSOMAL POSITION**

chr5:112175162

**VARIANT ALLELE FREQUENCY (% VAF)**

15.5%

potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP<sup>160-161</sup>. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days<sup>162</sup>; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386<sup>163-164</sup>.

alterations, as seen here, were observed to have significantly less T-cell inflammation in one study<sup>167</sup>.

**FINDING SUMMARY**

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation<sup>168</sup>. Alterations such as seen here may disrupt APC function or expression<sup>169-173</sup>.

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

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs<sup>159</sup>, and

**FREQUENCY & PROGNOSIS**

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset<sup>21</sup>. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples<sup>165</sup>. The prognostic significance of APC mutations in sporadic CRC remains unclear<sup>166</sup>. Solid tumors with WNT/beta-catenin pathway

**POTENTIAL GERMLINE IMPLICATIONS**

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)<sup>174-176</sup>. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth<sup>177</sup>, and in the appropriate clinical context germline testing of APC is recommended.

**GENE**

# ARAF

**ALTERATION**

amplification - equivocal

trametinib and the pan-RAF inhibitor sorafenib<sup>178</sup>. Furthermore, 1 patient with Stage 4 lung adenocarcinoma whose tumor harbored the activating ARAF mutation S214C experienced a near-complete response and 5-year PFS upon sorafenib treatment<sup>178</sup>.

**FINDING SUMMARY**

ARAF encodes a member of the RAF family of serine-threonine kinases that includes BRAF and CRAF and activates the MEK-ERK signaling cascade. Like CRAF, alteration of ARAF in cancer is thought to be rare compared to BRAF due to the requirement of activating phosphorylation of its negative-charge regulatory region<sup>180</sup>. ARAF overexpression and activating mutations have been reported to transform cultured cells and to hyperactivate the MEK-ERK MAPK pathway<sup>178</sup>. ARAF has been reported to be amplified in cancer<sup>181</sup> and may be biologically relevant in this context<sup>182-183</sup>.

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

ARAF activating mutations may predict sensitivity to pan-RAF and MEK inhibitors. In a preclinical study, cell transformation and hyperactivation of the MAPK pathway as a result of ARAF activation was reportedly inhibited by the MEK inhibitor

**FREQUENCY & PROGNOSIS**

ARAF mutation and amplification have been detected in 2% and 0.2% of cases in the MSKCC Metastatic Colorectal Cancer dataset, respectively<sup>179</sup>. Published data investigating the prognostic implications of ARAF alterations in colorectal cancer are limited (PubMed, Mar 2023).

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## GENOMIC FINDINGS

GENE  
**CCND2**

ALTERATION  
amplification

abemaciclib, palbociclib, and ribociclib. Clinical studies of CDK4/6 inhibitors have shown the most promise for estrogen receptor-positive breast cancer<sup>186-187</sup>.

associated with liver metastasis in colorectal cancer, and in patients with Stage 1 and 2 tumors, cyclin D2 expression has also been associated with reduced patient survival<sup>190</sup>.

**FREQUENCY & PROGNOSIS**

In the Colorectal Adenocarcinoma TCGA dataset, putative high-level amplification of CCND2 has been found in 1.4% of cases<sup>21</sup>. Cyclin D2 has also reportedly been overexpressed in 53% of colorectal adenocarcinomas<sup>188</sup>. Overexpression of CCND2 mRNA in CRC has been correlated with poor patient prognosis<sup>189</sup>. In addition, the expression of cyclin D2 at the invasive margin has been

**FINDING SUMMARY**

CCND2 encodes the protein cyclin D2, which binds and regulates the cyclin-dependent kinases that control cell cycle progression, and is a downstream target of cancer signaling pathways including hedgehog and PI3K<sup>191-192</sup>. CCND2 has been reported to be amplified in cancer<sup>181</sup>, and may be biologically relevant in this context<sup>182-183</sup>.

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

Although preclinical studies suggest that cyclin D2 activates CDK4/6<sup>184-185</sup>, it is unknown whether CCND2 amplification or activating mutation predicts response to CDK4/6 inhibitors such as

GENE  
**FGF23**

ALTERATION  
amplification

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>193</sup>.

sarcoma (4.3%), colorectal adenocarcinoma (4.2%), lung adenocarcinoma (3.7%), and head and neck squamous cell carcinoma (3.4%) (cBioPortal, 2023)<sup>181,194</sup>.

**FREQUENCY & PROGNOSIS**

FGF23 alterations have been reported with highest incidence in uterine carcinosarcoma (7.0%), ovarian carcinoma (6.5%), testicular germ cell cancer (5.4%), cutaneous melanoma (5.0%), low-grade glioma (4.9%), lung squamous cell carcinoma (4.5%),

**FINDING SUMMARY**

FGF23 encodes a member of the fibroblast growth factor protein family that plays a central role in phosphate homeostasis<sup>195</sup>. Overexpression of FGF23 by tumor cells can cause hypophosphatemia through excessive renal phosphate clearance<sup>196</sup>, while germline gain-of-function (protein stabilizing) mutations in FGF23 cause autosomal dominant hypophosphatemic rickets<sup>197</sup>.

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

There are no targeted therapies that directly address genomic alterations in FGF23. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest

GENE  
**FGF6**

ALTERATION  
amplification

12p13 (FGF6 and FGF23) experienced a radiologic CR<sup>193</sup>.

these genes in 1.3% of patients with breast cancer<sup>199</sup>. FGF6 expression has been reported in 54% (14/26) of prostate cancer samples, which also frequently express FGFR4<sup>200</sup>. FGF6 expression has also been observed in 71% (12/17) of patients with childhood acute lymphoblastic leukemia<sup>201</sup>.

**FREQUENCY & PROGNOSIS**

Somatic alterations affecting FGF6 are infrequently documented, with the highest rates reported in penile cancer (4%), cutaneous melanoma (1-3%), stomach carcinoma (1-3%) and colorectal cancer (1%) (cBioPortal, COSMIC, 2023)<sup>181,194,198</sup>. Amplification of FGF6 has been frequently observed in testicular germ cell cancer (5%) and ovarian serous cystadenocarcinoma (5%), and in 2-6% of lower-grade gliomas, glioblastomas, sarcomas, breast invasive carcinomas, uterine carcinosarcomas, lung squamous cell carcinomas (SCC), head and neck SCC, pancreatic adenocarcinomas, and esophageal carcinomas (cBioPortal, 2023)<sup>181,194</sup>. FGF6 is co-localized with FGF23 and CCND2 at chromosomal locus 12p13 and has been reported to be co-amplified with

**FINDING SUMMARY**

FGF6 (also known as HST-2) encodes a member of the fibroblast growth factor protein family and is hypothesized to play a role in muscle tissue regeneration<sup>202</sup> by signaling through FGFR4, and to a lesser extent FGFR1 and FGFR2<sup>203</sup>. FGF6 expression has been observed in several cancers<sup>200-201,204</sup> and was shown to be oncogenic in preclinical models<sup>204-205</sup>. FGF6 has been reported as amplified in cancer<sup>181</sup> and may be biologically relevant in this context<sup>182-183</sup>.

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

There are no targeted therapies that directly address genomic alterations in FGF6. 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

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GENOMIC FINDINGS

GENE  
**SMAD4**

ALTERATION  
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SMAD4. Preclinical studies in colorectal cancer have reported associations of SMAD4 inactivation or loss with sensitivity to inhibitors of Aurora kinase A<sup>206</sup> and the Wnt/beta-catenin pathway<sup>207</sup>.

— Nontargeted Approaches —

Clinical studies have reported associations of SMAD4 loss or low SMAD4 expression with improved responses to chemotherapeutic agents in patients with pancreatic cancer<sup>208-210</sup> and non-small cell lung cancer (NSCLC)<sup>211</sup>. Other clinical studies in pancreatic cancer have reported an association of high SMAD4 expression with better

responses to neoadjuvant chemotherapy<sup>212</sup> and adjuvant chemoradiotherapy<sup>213</sup>.

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)<sup>214</sup>, pancreatic acinar cell carcinoma (26%)<sup>215</sup>, cholangiocarcinoma (25%)<sup>216</sup>, small intestine cancer (20%)<sup>217</sup>, appendiceal adenocarcinoma (14-20% mutation; 57% deletion)<sup>218-219</sup>, colorectal adenocarcinoma (CRC; 14%)<sup>21</sup>, esophageal adenocarcinoma (14%)<sup>220</sup>, and stomach adenocarcinoma (13%)<sup>221</sup>. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)<sup>222</sup> and intraductal papillary mucinous neoplasms (IPMN)<sup>223</sup>; in clinical samples, SMAD4 homozygous deletion has been observed in 10% of IPMNs and 8% of MCNs, and mutation was also observed in 5% of IPMNs<sup>224</sup>. SMAD4 gene alterations have been associated with reduced OS for patients with pancreatic adenocarcinoma<sup>225</sup>. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types,

including CRC<sup>226-228</sup>, appendiceal mucinous neoplasm<sup>229</sup>, gastric adenocarcinoma<sup>230-231</sup>, esophageal adenocarcinoma<sup>232</sup>, esophageal squamous cell carcinoma<sup>233</sup>, breast cancer<sup>234</sup>, and prostate cancer<sup>235</sup>.

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling<sup>236-237</sup>. SMAD4 alterations that result in loss or disruption of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320) are predicted to be inactivating<sup>238-251</sup>.

POTENTIAL GERMLINE IMPLICATIONS

Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome<sup>252-254</sup>, which is associated with an increased risk of gastrointestinal cancers<sup>255</sup>. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65<sup>256</sup>. In the appropriate clinical context, germline testing of SMAD4 is recommended.

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THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

## Cetuximab

✖ Resistance of variant(s) to associated therapy is likely

Assay findings association

### KRAS

G12D

### NRAS

wildtype

### AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

### GENE ASSOCIATION

Therapies targeting EGFR, including cetuximab, have been shown to have significant clinical activity for patients with CRC<sup>110-113,257-258</sup>; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines, v3.2022, NCCN Rectal Cancer Guidelines, v4.2022). Activating mutations in either KRAS<sup>110-113</sup> or NRAS<sup>155,259</sup>, which function downstream of EGFR, are associated with lack of benefit of cetuximab for patients with CRC and indicate against the use of cetuximab (NCCN Colon Cancer Guidelines v3.2022).

### SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFIRI, FOLFOX4, or irinotecan<sup>110-111,257-258,260</sup> and as monotherapy for chemotherapy-refractory patients<sup>113,261</sup>. The Phase 3 study STRATEGIC-1 reported a similar duration of disease control (DDC) for patients with unresectable

metastatic CRC (mCRC) and KRAS-, NRAS-, and BRAF-wildtype status treated with mFOLFOX-bevacizumab alternated with a cetuximab regimen in first or second line, respectively (overall DDC 22.5 vs. 23.5 months); in addition, the study reported similar OS (37.8 vs. 34.4 months) and higher numerical ORR for patients treated with cetuximab in the first line followed by mFOLFOX-bevacizumab compared with those receiving EGFR-directed antibodies in the second or third line<sup>262</sup>. A prospective study of cetuximab monotherapy for patients with KRAS-, NRAS-, and BRAF-wildtype mCRC reported 11% (2/19) PRs and 58% (11/19) SDs<sup>263</sup>. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wildtype mCRC resulted in an ORR of 81% (4 CR and 27 PRs, n=37) and a DCR of 89%<sup>264</sup>. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)<sup>265</sup>. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)<sup>266</sup>.

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THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

## Panitumumab

✖ Resistance of variant(s) to associated therapy is likely

Assay findings association

### KRAS

G12D

### NRAS

wildtype

### AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

Therapies targeting EGFR, including panitumumab, have been shown to have significant clinical activity for patients with CRC<sup>114,265,267</sup>; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2022)(NCCN Rectal Cancers Guidelines, v4.2022). Activating mutations in either KRAS<sup>114-116</sup> or NRAS<sup>115,268</sup>, which function downstream of EGFR, are associated with lack of benefit of panitumumab for patients with CRC and indicate against the use of panitumumab (NCCN Colon Cancer Guidelines v3.2022, NCCN Rectal Cancer Guidelines v4.2022).

### SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFOX4, FOLFIRI, irinotecan, or best supportive care<sup>114,269-272</sup>, and as

monotherapy for chemotherapy-refractory patients<sup>265,267-268</sup>. The Phase 3 PARADIGM trial comparing panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 as first-line treatment for patients with RAS-wildtype left-sided metastatic CRC demonstrated that treatment with panitumumab significantly improved median OS (mOS; 36.2 months vs. 31.3 months) compared with bevacizumab<sup>273</sup>. A Phase 2 trial reported that, for patients with unresectable RAS-wildtype colorectal adenocarcinoma treated with panitumumab plus FOLFOX4, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS OF 59% vs. 49%)<sup>274</sup>. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)<sup>265</sup>. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)<sup>266</sup>.

**NOTE** Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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CLINICAL TRIALS

**NOTE** 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. 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 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://www.clinicaltrials.gov). Or, visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

## GENE

APC

## ALTERATION

Q1291\*

## RATIONALE

Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

## NCT04008797

## PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

## TARGETS

CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

**LOCATIONS:** Taipei (Taiwan), Tainan (Taiwan), Kurume (Japan), Matsuyama (Japan), Seongnam-si Bundang (Korea, Republic of), Songpa-gu (Korea, Republic of), Seodaemun (Korea, Republic of), Seoul (Korea, Republic of), Jongno-gu (Korea, Republic of), Osakasayama (Japan)

## NCT05091346

## PHASE 1/2

A Study of E7386 in Combination With Pembrolizumab in Previously Treated Participants With Selected Solid Tumors

## TARGETS

CBP, Beta-catenin, PD-1

**LOCATIONS:** Fukuoka (Japan), Osaka (Japan), Shizuoka (Japan), Tokyo (Japan), Chiba-shi (Japan), Kashiwa (Japan), Sapporo-shi (Japan), Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom)

## NCT03264664

## PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

## TARGETS

CBP, Beta-catenin

**LOCATIONS:** Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), California, Arizona, Minnesota

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**CLINICAL TRIALS**
**GENE**
**ARAF**
**ALTERATION**
**amplification - equivocal**
**RATIONALE**

ARAF activating mutations may lead to increased RAF activity and subsequent activation of the MEK pathway and may predict sensitivity to therapies targeting these pathways.

**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

**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)

**NCT03905148**
**PHASE 1/2**

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

**TARGETS**

RAFs, EGFR, MEK

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

**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)

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**CLINICAL TRIALS**
**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

**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)

**NCT04817956**
**PHASE 2**

Improving Public Cancer Care by Implementing Precision Medicine in Norway

**TARGETS**  
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

**LOCATIONS:** Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

**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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**CLINICAL TRIALS**
**GENE**
**CCND2**
**RATIONALE**

CCND2 amplification or activation may predict sensitivity to CDK4/6 inhibitors.

**ALTERATION**
**amplification**
**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)

**NCT05480280**
**PHASE 2**

mFOLFOX6 Combined With Dalpiciclib in Patients With Metastatic Colorectal Cancer

**TARGETS**

CDK6, CDK4

**LOCATIONS:** Guangzhou (China)

**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)

**NCT03994796**
**PHASE 2**

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

**TARGETS**

TRKB, ALK, TRKC, ROS1, TRKA, CDK4, CDK6, PI3K, mTOR

**LOCATIONS:** Washington, Oregon, Idaho, Montana

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

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

**TARGETS**

ER, CDK4, CDK6, CDK2

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

**NCT02896335**
**PHASE 2**

Palbociclib In Progressive Brain Metastases

**TARGETS**

CDK4, CDK6

**LOCATIONS:** Massachusetts

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**CLINICAL TRIALS**
**NCT03310879**
**PHASE 2**

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

**TARGETS**  
CDK4, CDK6

**LOCATIONS:** Massachusetts

**NCT03454035**
**PHASE 1**

Ulixertinib/Palbociclib in Patients With Advanced Pancreatic and Other Solid Tumors

**TARGETS**  
CDK4, CDK6, ERK2, ERK1

**LOCATIONS:** North Carolina

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

**ORDERED TEST #** ORD-1638953-01

**CLINICAL TRIALS**
**GENE**
**KRAS**
**ALTERATION**
**G12D**
**RATIONALE**

KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS mutation may predict sensitivity to PLK1 inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors. Preclinical and clinical evidence suggest that KRAS G12D

mutations may confer sensitivity to KRAS G12D-targeted, T-cell-receptor-based adoptive cell therapy, KRAS G12D small-molecule inhibitors, or SOS1 inhibitors. Multiple clinical studies have reported lack of efficacy of MEK inhibitors as monotherapy for treatment of KRAS-mutant colorectal cancer; combination therapies may be more effective.

**NCT05533463**
**PHASE 1**

Phase I Study of HRS-4642 in Patients With Advanced Solid Tumors Harboring KRAS G12D Mutation

**TARGETS**  
KRAS

**LOCATIONS:** ShangHai (China)

**NCT05438667**
**PHASE NULL**

TCR-T Cell Therapy on Advanced Pancreatic Cancer and Other Solid Tumors

**TARGETS**  
KRAS

**LOCATIONS:** Guangzhou (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

**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)

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Electronically signed by Erik Williams, M.D. | 05 June 2023  
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**ORDERED TEST #** ORD-1638953-01

**CLINICAL TRIALS**
**NCT04303403**
**PHASE 1**

Study of Trametinib and Ruxolitinib in Colorectal Cancer and Pancreatic Adenocarcinoma

**TARGETS**  
JAK2, JAK1, MEK

**LOCATIONS:** Singapore (Singapore)

**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

**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

**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)

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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.

**ATM**

 NM\_000051.3: c.3635C>T  
(p.S1212F)  
chr11:108153495

**CSF1R**

 NM\_005211.3: c.1862C>T  
(p.T621M)  
chr5:149440532

**FGF12**

 NM\_021032.4: c.298A>T  
(p.N100Y)  
chr3:192078229

**KDM5C**

 NM\_004187.3: c.3434C>T  
(p.S1145F)  
chrX:53224117

**MED12**

 NM\_005120.2: c.3785G>A  
(p.R1262K)  
chrX:70349623

**MSH3**

 NM\_002439.3: c.1606A>G  
(p.T536A)  
chr5:80037320

**P2RY8**

 NM\_178129.4: c.908G>A  
(p.R303H)  
chrX:1584544

**RAD52**

amplification

**RAD54L**

 NM\_003579.3: c.1264G>C  
(p.E422Q)  
chr1:46738363

**RPTOR**

 NM\_020761.2: c.434G>A  
(p.R145Q)  
chr17:78681726

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**APPENDIX**

Genes Assayed in FoundationOne®CDx

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

**DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS**

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B or WTX)	
APC	AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX
AURKA	AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2
BCL6	BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1
BTG2	BTK	CALR	CARD11	CASP8	CBFB	CBL	CCND1	CCND2
CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73	CDH1
CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R	CTCF
CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1	DDR2
DIS3	DNMT3A	DOT1L	EED	EGFR	EMSY (C11orf30)	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14
FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3	GATA4
GATA6	GID4 (C17orf39)	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3-3A (H3F3A)
HDAC1	HGF	HNFA1	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	MRE11 (MRE11A)	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD2 (WHSC1 or MMSET)	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3	NTRK3
P2RY8	PALB2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)
PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1
PMS2	POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI
PRKN (PARK2)	PTCH1	PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51
RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10
REL	RET	RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC
SDHD	SETD2	SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO
SNCAIP	SOC1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3
STK11	SUFU	SYK	TBX3	TEK	TENT5C (FAM46C)	TET2	TET2	TGFB2
TIPARP	TNFAIP3	TNFRSF14	TP53	TSC1	TSC2	TYRO3	U2AF1	VEGFA
VHL	WT1	XPO1	XRCC2	ZNF217	ZNF703			

**DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS**

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	ETV4
ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KIT	KMT2A (MLL)
MSH2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSP02	SDC4	SLC34A2	TERC*	TERT**	TPRSS2

\*TERC is an NCRNA

\*\*Promoter region of TERT is interrogated

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


Homologous Recombination status  
Loss of Heterozygosity (LOH) score  
Microsatellite (MS) status  
Tumor Mutational Burden (TMB)

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## APPENDIX

## About FoundationOne®CDx

FoundationOne 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, Ciplstraat 3, 2440 Geel, Belgium. 

## ABOUT FOUNDATIONONE CDx

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne 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:  
[www.rochefoundationmedicine.com/f1cdxtech](http://www.rochefoundationmedicine.com/f1cdxtech).

## INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx 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 solid malignant neoplasms.

## TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes

detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture-selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g. gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

## 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. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. 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.

### Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

### Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical

methodology has identified as being present in <10% of the assayed tumor DNA.

## 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.

## 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.

## Limitations

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

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## APPENDIX

## About FoundationOne®CDx

- analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.
- TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation [https://www.accessdata.fda.gov/cdrh\\_docs/pdf17/P170019B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf). The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
  - Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score  $\geq 16$  will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
  - The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and

- extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
- Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
  - Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
  - Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in <https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/> report the frequency of *HER2* overexpression as 20% in breast cancer. Based on the F1CDx *HER2* CDx concordance study, approximately 10% of *HER2* amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

### 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.

### VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	%CV*
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

\*Interquartile Range = 1st Quartile to 3rd Quartile

### 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 >10%, 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

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**APPENDIX**

About FoundationOne®CDx

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*, *CBL*, *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.

**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 CDx.

**TREATMENT DECISIONS ARE 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 or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

**SELECT ABBREVIATIONS**

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
mut/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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ORDERED TEST # **ORD-1638953-01**
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