

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

<b>PATIENT</b>	<b>DISEASE</b> Colon adenocarcinoma (CRC)	<b>PHYSICIAN</b>	<b>ORDERING PHYSICIAN</b> Yeh, Yi-Chen	<b>SPECIMEN</b>	<b>SPECIMEN SITE</b> Colon
	<b>NAME</b> Tsai, Min-Kuang		<b>MEDICAL FACILITY</b> Taipei Veterans General Hospital		<b>SPECIMEN ID</b> S110-34022C (PF22008)
	<b>DATE OF BIRTH</b> 15 January 1942		<b>ADDITIONAL RECIPIENT</b> None		<b>SPECIMEN TYPE</b> Slide Deck
	<b>SEX</b> Male		<b>MEDICAL FACILITY ID</b> 205872		<b>DATE OF COLLECTION</b> 09 November 2021
	<b>MEDICAL RECORD #</b> 11555478		<b>PATHOLOGIST</b> Not Provided		<b>SPECIMEN RECEIVED</b> 27 January 2022

## 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** G13D  
**NRAS** wildtype  
**APC** R283\*, E1451fs\*25  
**FBXW7** R465C  
**MYC** amplification  
**SMAD2** loss  
**TP53** R175H

2 Disease relevant genes with no reportable alterations: **BRAF**, **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. 9)
- 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

### THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section





No therapies or clinical trials. see Biomarker Findings section


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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
<b>KRAS</b> - G13D	<b>Cetuximab</b> 	none
10 Trials see p. 14	<b>Panitumumab</b> 	
<b>NRAS</b> - wildtype	<b>Cetuximab</b> 	none
0 Trials	<b>Panitumumab</b> 	
<b>APC</b> - R283*, E1451fs*25	none	none
4 Trials see p. 11		
<b>FBXW7</b> - R465C	none	none
7 Trials see p. 12		
<b>MYC</b> - amplification	none	none
4 Trials see p. 16		

 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.

**SMAD2** - loss ..... p. 7    **TP53** - R175H ..... p. 8

**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, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors<sup>34-37,44</sup>. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors<sup>34</sup>. 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>45</sup> or those with lower TMB treated with PD-1 or PD-L1-targeting agents<sup>35</sup>. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with

TMB  $\geq 10$  Muts/Mb (based on this assay or others) compared to those with TMB  $< 10$  Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials<sup>37,44</sup>. Together, these studies suggest that patients with TMB  $\geq 10$  Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. 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>46</sup>.

## FREQUENCY & PROGNOSIS

Elevated tumor mutational burden (TMB) has been reported in 8-25% of colorectal cancer (CRC) samples<sup>21,47-48</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>21,47</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>47</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>21,47</sup>. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB<sup>21,47</sup>, whereas TMB-low tumors more frequently harbor mutations in TP53 and APC<sup>21</sup>. In a study for 61 patients with metastatic, microsatellite stable (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 as compared with plasma TMB scores  $< 28$  muts/Mb (3.0 vs. 5.3 months, HR 0.76,  $p=0.007$ ), whereas tissue TMB was not found to be prognostic in this population<sup>49</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>50-51</sup> and cigarette smoke in lung cancer<sup>52-53</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>54-55</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>21,56-59</sup>, and microsatellite instability (MSI)<sup>21,56,59</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>34,44,46</sup>.

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## GENOMIC FINDINGS

## GENE

## KRAS

## ALTERATION

G13D

## TRANSCRIPT ID

NM\_004985

## CODING SEQUENCE EFFECT

38G&gt;A

## VARIANT ALLELE FREQUENCY (% VAF)

38.3%

## 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>60-65</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>66-70</sup>. Both clinical<sup>71-72</sup> and preclinical<sup>73-74</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>72</sup>, RAF inhibitors<sup>73</sup>, pan-ERBB inhibitors<sup>74</sup>, or chemotherapeutic agents<sup>71</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>75</sup>. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated low-grade serous ovarian cancer and 12% (2/17) for patients with KRAS-mutated non-small cell lung cancer (NSCLC) in a Phase 1 study<sup>76-77</sup>. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors<sup>78-79</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>80</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>81</sup>. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors<sup>82-83</sup>. Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations<sup>84-85</sup>. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors<sup>86</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>87</sup>.

## — Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab<sup>88-91</sup> or panitumumab<sup>92-94</sup> for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v3.2021).

## FREQUENCY &amp; PROGNOSIS

Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)<sup>95-103</sup>. Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC<sup>97-100,104-105</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>61,106</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, R68S, and K117N have been characterized as activating and oncogenic<sup>61,107-129</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>88-91</sup> or panitumumab<sup>92-94</sup> for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v3.2021).

## FREQUENCY &amp; PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations<sup>21,103,130-135</sup>. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis<sup>103</sup> and longer survival<sup>135-136</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>61</sup>. No alterations in NRAS were identified in this case.

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**GENOMIC FINDINGS**
**GENE**

# APC

**ALTERATION**

R283\*, E1451fs\*25

**TRANSCRIPT ID**

NM\_000038, NM\_000038

**CODING SEQUENCE EFFECT**

847C&gt;T, 4350\_4351insCCAAGCGA

**VARIANT ALLELE FREQUENCY (% VAF)**

18.9%, 38.8%

**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>137</sup>, and 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>138-139</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>140</sup>; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386<sup>141-142</sup>.

**FREQUENCY & PROGNOSIS**

APC alterations have been found in 77% of tumors in the Colorectal Adenocarcinoma TCGA dataset<sup>21</sup>. Inactivation of APC leads to activation of the Wnt/beta-catenin pathway, which is thought to play a role in the adenoma-carcinoma transition in some cancers, including colorectal cancer (CRC)<sup>143</sup>. The prognostic significance of APC mutations in sporadic CRC remains unclear<sup>144</sup>. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study<sup>145</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>146</sup>. Alterations such as seen here may disrupt APC function or expression<sup>147-151</sup>.

**POTENTIAL GERMLINE IMPLICATIONS**

One or more of the APC 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 familial adenomatous polyposis (ClinVar, Sep 2021)<sup>152</sup>. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)<sup>153-155</sup>. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth<sup>156</sup>, and in the appropriate clinical context germline testing of APC is recommended.

**GENE**

# FBXW7

**ALTERATION**

R465C

**TRANSCRIPT ID**

NM\_033632

**CODING SEQUENCE EFFECT**

1393C&gt;T

**VARIANT ALLELE FREQUENCY (% VAF)**

32.8%

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

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors<sup>157-158</sup>. Several case studies reported clinical benefit for patients with FBXW7-mutated cancers, including lung

adenocarcinoma<sup>159</sup>, renal cell carcinoma<sup>160</sup>, and cervical squamous cell carcinoma<sup>161</sup>.

**— Potential Resistance —**

Multiple clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies to treat CRC, even for tumors that harbor alterations in PIK3CA or PTEN; data are more limited for alterations in other genes in this pathway<sup>162-164</sup>.

**— Nontargeted Approaches —**

FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies<sup>165</sup>.

**FREQUENCY & PROGNOSIS**

Mutations in FBXW7 have been identified in 9-21% of colorectal adenocarcinomas<sup>21,166-167</sup> and

also in 4-7% of colorectal adenomas<sup>168-169</sup>. FBXW7 has been reported to be the fourth most commonly mutated gene in colorectal cancer, with mutations in 6-10% of cases in the scientific literature<sup>168,170-171</sup>. Low FBXW7 mRNA levels are associated with poor patient prognosis, and FBXW7 inactivation in colorectal cancer has been associated with chromosomal instability<sup>168,172</sup>.

**FINDING SUMMARY**

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation<sup>173</sup>. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor<sup>173-174</sup>. Alterations such as seen here may disrupt FBXW7 function or expression<sup>174-181</sup>.

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**GENOMIC FINDINGS**
**GENE**

# MYC

**ALTERATION**  
 amplification

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

There are no available therapies that directly target MYC. However, preclinical data indicate that MYC overexpression may predict sensitivity to investigational agents targeting CDK1<sup>182-183</sup>, CDK2<sup>184</sup>, Aurora kinase A<sup>185-192</sup>, Aurora kinase B<sup>193-196</sup>, glutaminase<sup>197-200</sup>, or BET bromodomain-containing proteins<sup>201-204</sup>, as well as agents targeting both HDAC and PI3K<sup>205-207</sup>. A Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer but not for patients without MYC overexpression<sup>208</sup>. A patient with MYC-amplified

invasive ductal breast carcinoma experienced a PR to an Aurora kinase inhibitor<sup>209</sup>. The glutaminase inhibitor CB-839, in combination with either everolimus or cabozantinib, has demonstrated encouraging efficacy in Phase 1 and 2 studies enrolling patients with pretreated advanced renal cell carcinoma<sup>210-211</sup>.

**— Nontargeted Approaches —**

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies<sup>212-213</sup>. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel<sup>214-215</sup>.

**FREQUENCY & PROGNOSIS**

Mutation and amplification of MYC have been observed in up to 2% and 5% of patients with colorectal cancer, respectively (cBioPortal, COSMIC, Sep 2021)<sup>216-218</sup>. Overexpression of MYC in colorectal carcinoma has been reported to occur in the absence of MYC amplification<sup>219-221</sup>. MYC is

a target gene of beta-catenin and may be upregulated by aberrant WNT signaling in colorectal cancer<sup>222</sup>. MYC overexpression has been reported in 62-91% of colorectal carcinomas studied<sup>219,221,223-224</sup>. MYC protein overexpression was reported to be a favorable prognostic biomarker in patients with colorectal cancer, and patients with low-level MYC amplification have been found to have significantly longer survival<sup>224-225</sup>. However, MYC amplification and high expression have been associated with metastatic and aggressive colorectal tumors<sup>221,226</sup>.

**FINDING SUMMARY**

MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers<sup>227</sup>. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types<sup>228</sup>. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes<sup>227,229-230</sup>.

**GENE**

# SMAD2

**ALTERATION**  
 loss

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

There are no therapies that target the loss of SMAD2 or loss of TGF-beta signaling in cancer. Because TGF-beta can exert both tumor suppressor as well as pro-tumor effects, the development of therapies aimed at this pathway must be carefully considered for each patient. In

preclinical studies, several novel small-molecule TGF-beta pathway inhibitors have been shown to reduce SMAD2 phosphorylation and tumor invasion in breast cancer cells and to increase survival in mouse xenograft models<sup>231-232</sup>.

**FREQUENCY & PROGNOSIS**

SMAD2 mutations have been reported in various tumor types, including cutaneous squamous cell carcinoma (SCC; 6-10%)<sup>233</sup>, colorectal adenocarcinoma (CRC; 3-7%)<sup>21,234</sup>, endometrial cancers (2-5%)<sup>56</sup>, stomach adenocarcinoma (2-3%)<sup>235</sup>, lung SCC (1-2%)<sup>236</sup>, and lung adenocarcinoma (1-2%)<sup>237-240</sup>. SMAD2 deletion, as well as loss of expression or phosphorylation (p-SMAD2), has been reported in several

cancers<sup>241-247</sup> and has been correlated with poor prognosis in hepatocellular, gastric, breast, and colorectal cancer<sup>242-246</sup> but good prognosis in HNSCC<sup>248-249</sup>.

**FINDING SUMMARY**

SMAD2 encodes an intracellular transducer that is activated by TGF-beta or activin to dimerize with SMAD4 and regulate transcription of TGF-beta or activin-activated genes<sup>250-251</sup>. SMAD2 alterations that disrupt the MH1 domain (amino acids 10-176), MH2 domain (amino acids 274-467), or critical phosphorylation sites are predicted to result in a loss of function<sup>234,247,252-255</sup>.

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ORDERED TEST # ORD-1286663-01

## GENOMIC FINDINGS

## GENE

## TP53

## ALTERATION

R175H

## TRANSCRIPT ID

NM\_000546

## CODING SEQUENCE EFFECT

524G&gt;A

## VARIANT ALLELE FREQUENCY (% VAF)

39.9%

## 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>256-259</sup>, or p53 gene therapy and immunotherapeutics such as SGT-53<sup>260-264</sup> and ALT-801<sup>265</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>266</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>267</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>268</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>269</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>270</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>271</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>272</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>264</sup>. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246<sup>273-275</sup>. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR<sup>276</sup>. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies<sup>277-278</sup>; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies<sup>279-280</sup>. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

## FREQUENCY &amp; PROGNOSIS

TP53 mutations have been reported in up to 60% of colorectal cancer cases<sup>21,281-286</sup>. A study reported p53 expression in 49% of analyzed colorectal cancer cases<sup>287</sup>. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC<sup>288</sup>.

## FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers<sup>289</sup>. Alterations such

as seen here may disrupt TP53 function or expression<sup>290-294</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 2021)<sup>152</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>295-297</sup>, including sarcomas<sup>298-299</sup>. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000<sup>300</sup> to 1:20,000<sup>299</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>301</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>302-307</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>302-303</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>308</sup>. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH<sup>306,309-310</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.



ORDERED TEST # ORD-1286663-01

THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

## Cetuximab

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

Assay findings association

**KRAS**  
G13D

**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>88-91,311-312</sup>; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2021). Activating mutations in either KRAS<sup>88-91</sup> or NRAS<sup>133,286</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 Guidelines v3.2021). Activating mutations in either KRAS<sup>88-91</sup> or NRAS<sup>133,286</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 v3.2021).

### SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and

response rate for patients with KRAS-wild-type CRC, both as first-line combination therapy with FOLFIRI or FOLFOX<sub>4</sub><sup>88-89,312</sup> and as monotherapy or combination therapy with irinotecan for chemotherapy-refractory patients<sup>90-91,311</sup>. A prospective study of first-line cetuximab for patients with KRAS/NRAS/BRAF mutation-negative metastatic CRC resulted in limited efficacy, with 10.5% (2/19) of participants experiencing PRs and 57.9% (11/19) experiencing SDs<sup>313</sup>. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wild-type metastatic CRC resulted in an ORR of 79.5% (6 CR and 25 PRs, n=39) and a DCR of 92.3%<sup>314</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>315</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>316</sup>.

## Panitumumab

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

Assay findings association

**KRAS**  
G13D

**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>92,315,317</sup>; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2021). Activating mutations in either KRAS<sup>92-94</sup> or NRAS<sup>93,284</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 Guidelines v3.2021). Activating mutations in either KRAS<sup>92-94</sup> or NRAS<sup>93,284</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, v3.2021).

### SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS wild-type CRC, both as first-line combination therapy with FOLFOX<sub>4</sub><sup>92</sup> and as monotherapy for chemotherapy-refractory patients<sup>315,317</sup>. An open-label, randomized Phase 2 trial reported that for patients with unresectable RAS-wild-type colorectal adenocarcinoma treated with first-line panitumumab plus FOLFOX<sub>4</sub>, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS 59% vs. 49%)<sup>318</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>315</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>316</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

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THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

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

**GENE**  
**APC**
**ALTERATION**

R283\*, E1451fs\*25

**RATIONALE**

Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to

CBP/beta-catenin interaction inhibitors.

**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:** Tokyo (Japan)

**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:** Osakasayama (Japan), Chuo-Ku (Japan), Kashiwa (Japan)

**NCT03833700**
**PHASE 1**

A Study of E7386 in Participants With Advanced Solid Tumor Including Colorectal Cancer (CRC)

**TARGETS**

CBP, Beta-catenin

**LOCATIONS:** Chuo Ku (Japan), Kashiwa (Japan)

**NCT03264664**
**PHASE 1**

Study of E7386 in Participants With Selected Advanced Neoplasms

**TARGETS**

CBP, Beta-catenin

**LOCATIONS:** Glasgow (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom)

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**CLINICAL TRIALS**
**GENE**
**FBXW7**
**ALTERATION**
**R465C**
**RATIONALE**

Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors. Several clinical studies have shown that inhibitors of the PI3K-AKT-mTOR pathway have not produced

significant clinical benefit when used as a monotherapy in patients with colorectal cancer; combination therapies may be required to overcome this lack of response.

**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)

**NCT03217669**
**PHASE 1**

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

**TARGETS**  
IDO1, mTOR

**LOCATIONS:** Kansas

**NCT03065062**
**PHASE 1**

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

**TARGETS**  
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

**LOCATIONS:** Massachusetts

**NCT01582191**
**PHASE 1**

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

**TARGETS**  
mTOR, EGFR, SRC, RET, VEGFRs

**LOCATIONS:** Texas

**NCT02159989**
**PHASE 1**

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

**TARGETS**  
VEGFA, VEGFB, PIGF, mTORC1, mTORC2

**LOCATIONS:** Texas

**NCT02321501**
**PHASE 1**

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

**TARGETS**  
ROS1, ALK, mTOR

**LOCATIONS:** Texas

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**CLINICAL TRIALS**
**NCT03017833**
**PHASE 1**

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

**TARGETS**  
 mTORC1, mTORC2

**LOCATIONS:** Texas

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**CLINICAL TRIALS**
**GENE**
**KRAS**
**ALTERATION**
**G13D**
**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. 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.

**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)

**NCT03989115**
**PHASE 1/2**

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

**TARGETS**

SHP2, MEK

**LOCATIONS:** Seoul (Korea, Republic of), Oregon, California, Colorado, Arizona, Wisconsin, Illinois

**NCT03284502**
**PHASE 1**

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

**TARGETS**

MEK, RAFs

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

**NCT04303403**
**PHASE 1**

Study of Trametinib and Ruxolitinib in Colorectal Cancer and Pancreatic Adenocarcinoma

**TARGETS**

JAK2, JAK1, MEK

**LOCATIONS:** Singapore (Singapore)

**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)

**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), Texas

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**CLINICAL TRIALS**
**NCT03829410**
**PHASE 1/2**

Onvansertib in Combination With FOLFIRI and Bevacizumab for Second Line Treatment of Metastatic Colorectal Cancer Patients With a Kras Mutation

**TARGETS**  
 PLK1, VEGFA

**LOCATIONS:** California, Arizona, Minnesota, Kansas, Arkansas, Virginia, Florida

**NCT02079740**
**PHASE 1/2**

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

**TARGETS**  
 BCL2, BCL-XL, BCL-W, MEK

**LOCATIONS:** Massachusetts

**NCT04111458**
**PHASE 1**

A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation)

**TARGETS**  
 KRAS, SOS1, MEK

**LOCATIONS:** Frankfurt am Main (Germany), Köln (Germany), Utrecht (Netherlands), Rotterdam (Netherlands), Massachusetts, Tennessee, Texas, North Carolina

**NCT02407509**
**PHASE 1**

Phase I Trial of RO5126766

**TARGETS**  
 RAFs, MEK, mTOR

**LOCATIONS:** London (United Kingdom), Sutton (United Kingdom)

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**CLINICAL TRIALS**
**GENE**
**MYC**
**ALTERATION**
**amplification**
**RATIONALE**

MYC overexpression may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, including Aurora kinase A and B,

and of BET domain proteins, which are reported to downregulate MYC expression and MYC-dependent transcriptional programs.

**NCT03220347**
**PHASE 1**

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

**TARGETS**

**BRD2, BRD3, BRD4, BRDT**

**LOCATIONS:** Kashiwa (Japan), Meldola (Italy), Napoli, Campania (Italy), Rozzano (MI) (Italy), Villejuif (France), Bordeaux (France), Barcelona (Spain), Madrid (Spain)

**NCT03297424**
**PHASE 1/2**

A Study of PLX2853 in Advanced Malignancies.

**TARGETS**

**BRD4**

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

**NCT04555837**
**PHASE 1/2**

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

**TARGETS**

**Aurora kinase A, PD-1**

**LOCATIONS:** Texas

**NCT01434316**
**PHASE 1**

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

**TARGETS**

**PARP, CDK1, CDK9, CDK5, CDK2**

**LOCATIONS:** Massachusetts

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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.

**ERBB3**  
F219L

**LYN**  
amplification

**MSH3**  
P63\_P64insAAPPAP

**NBN**  
amplification

**NTRK1**  
V99M

**RAD21**  
amplification

**SDHA**  
V406M

**STK11**  
F354L

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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)	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	C11orf30 (EMSY)	C17orf39 (GID4)	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	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FAM46C	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	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3F3A
HDAC1	HGF	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDMSA	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	MKKN1	MLH1	MPL	MRE11A	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKB1A	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD3 (WHSC1L1)	NTSC2	NTRK1	NTRK2	NTRK3	P2RY8	PALB2
PARK2	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	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	SOC3
SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3	STK11	SUFU
SYK	TBX3	TEK	TET2	TGFBR2	TIPARP	TNFAIP3	TNFRSF14	TP53
TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL	WHSC1	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**	TMPRSS2

\*TERC is an NCRNA

\*\*Promoter region of TERT is interrogated

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

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, Cipalstraat 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 PRINCIPLES**

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. 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.

**Limitations**

1. In the fractional-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 analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

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About FoundationOne®CDx

- 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.
  - 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 = 1<sup>st</sup> Quartile to 3<sup>rd</sup> 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; 291656669) 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 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

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About FoundationOne®CDx

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

MR Suite Version 6.0.0

The median exon coverage for this sample is 848x

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**APPENDIX** **References**

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) PMID: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) PMID: 26140250
3. Lal N, et al. Oncoimmunology (2015) PMID: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) PMID: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Ciardiello et al., 2018; ESMO Abstract LBA-004
7. Parikh et al., 2021; DOI: 10.1038/s43018-021-00269-7
8. Fukuoka S, et al. J. Clin. Oncol. (2020) PMID: 32343640
9. Kim et al., 2020; DOI: 10.1016/j.jannonc.2020.04.073
10. Zhang Y, et al. BMC Gastroenterol (2021) PMID: 34688262
11. Sinicrope FA, et al. J. Clin. Oncol. (2013) PMID: 24019539
12. Gavin PG, et al. Clin. Cancer Res. (2012) PMID: 23045248
13. Bertagnolli MM, et al. J. Clin. Oncol. (2009) PMID: 19273709
14. Van Cutsem E, et al. J. Clin. Oncol. (2009) PMID: 19451425
15. Ribic CM, et al. N. Engl. J. Med. (2003) PMID: 12867608
16. Sargent DJ, et al. J. Clin. Oncol. (2010) PMID: 20498393
17. Fallik D, et al. Cancer Res. (2003) PMID: 14522894
18. Guastadisegni C, et al. Eur. J. Cancer (2010) PMID: 20627535
19. Pawlik TM, et al. Dis. Markers (2004) PMID: 15528785
20. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) PMID: 26337942
21. Nature (2012) PMID: 22810696
22. Histopathology (2007) PMID: 17204026
23. Samowitz WS, et al. Cancer Epidemiol. Biomarkers Prev. (2001) PMID: 11535541
24. Elsaleh H, et al. Clin Colorectal Cancer (2001) PMID: 12445368
25. Brueckl WM, et al. Anticancer Res. (2012) PMID: 22820457
26. Guidoboni M, et al. Am. J. Pathol. (2001) PMID: 11438476
27. Gryfe R, et al. N. Engl. J. Med. (2000) PMID: 10631274
28. Sinicrope FA, et al. Gastroenterology (2006) PMID: 16952542
29. Laghi L, et al. Dig Dis (2012) PMID: 22722556
30. You JF, et al. Br. J. Cancer (2010) PMID: 21081928
31. Bairwa NK, et al. Methods Mol. Biol. (2014) PMID: 24623249
32. Boland CR, et al. Cancer Res. (1998) PMID: 9823339
33. Boland CR, et al. Gastroenterology (2010) PMID: 20420947
34. Samstein RM, et al. Nat. Genet. (2019) PMID: 30643254
35. Goodman AM, et al. Mol. Cancer Ther. (2017) PMID: 28835386
36. Goodman AM, et al. Cancer Immunol Res (2019) PMID: 31405947
37. Cristescu R, et al. Science (2018) PMID: 30309915
38. Ready N, et al. J. Clin. Oncol. (2019) PMID: 30785829
39. Hellmann MD, et al. N. Engl. J. Med. (2018) PMID: 29658845
40. Hellmann MD, et al. Cancer Cell (2018) PMID: 29657128
41. Hellmann MD, et al. Cancer Cell (2018) PMID: 29731394
42. Rozeman EA, et al. Nat Med (2021) PMID: 33558721
43. Sharma P, et al. Cancer Cell (2020) PMID: 32916128
44. Marabelle A, et al. Lancet Oncol. (2020) PMID: 32919526
45. Legrand et al., 2018; ASCO Abstract 12000
46. Fabrizio DA, et al. J Gastrointest Oncol (2018) PMID: 30151257
47. Stadler ZK, et al. J. Clin. Oncol. (2016) PMID: 27022117
48. Shao C, et al. JAMA Netw Open (2020) PMID: 33119110
49. Chen EX, et al. JAMA Oncol (2020) PMID: 32379280
50. Pfeifer GP, et al. Mutat. Res. (2005) PMID: 15748635
51. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) PMID: 23875803
52. Pfeifer GP, et al. Oncogene (2002) PMID: 12379884
53. Rizvi NA, et al. Science (2015) PMID: 25765070
54. Johnson BE, et al. Science (2014) PMID: 24336570
55. Choi S, et al. Neuro-oncology (2018) PMID: 29452419
56. Cancer Genome Atlas Research Network, et al. Nature (2013) PMID: 23636398
57. Briggs S, et al. J. Pathol. (2013) PMID: 23447401
58. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) PMID: 24583393
59. Roberts SA, et al. Nat. Rev. Cancer (2014) PMID: 25568919
60. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) PMID: 6320174
61. Pylyayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) PMID: 21993244
62. Yamaguchi T, et al. Int. J. Oncol. (2011) PMID: 21523318
63. Watanabe M, et al. Cancer Sci. (2013) PMID: 23438367
64. Gilmartin AG, et al. Clin. Cancer Res. (2011) PMID: 21245089
65. Yeh JJ, et al. Mol. Cancer Ther. (2009) PMID: 19372556
66. Tsimberidou et al., 2013; ASCO Abstract e22086
67. Infante JR, et al. Lancet Oncol. (2012) PMID: 22805291
68. Zimmer L, et al. Clin. Cancer Res. (2014) PMID: 24947927
69. Bannouna J, et al. Invest New Drugs (2011) PMID: 20127139
70. Weekes CD, et al. Clin. Cancer Res. (2013) PMID: 23434733
71. Hochster et al., 2013; ASCO GI Abstract 380
72. Juric et al., 2014; ASCO Abstract 9051
73. Lamba S, et al. Cell Rep (2014) PMID: 25199829
74. Sun C, et al. Cell Rep (2014) PMID: 24685132
75. Guo C, et al. Lancet Oncol (2020) PMID: 33128873
76. Krebs et al., 2021; AACR Abstract CT019
77. Shinde et al., 2020; AACR Abstract CT143
78. Lu H, et al. Mol Cancer Ther (2019) PMID: 31068384
79. Mainardi S, et al. Nat Med (2018) PMID: 29808006
80. Koczywas et al., 2021; AACR Abstract LB001
81. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
82. Hillig RC, et al. Proc Natl Acad Sci U S A (2019) PMID: 30683722
83. Hofmann MH, et al. Cancer Discov (2021) PMID: 32816843
84. Hofmann et al., 2021; AACR Abstract CT210
85. Gort et al., 2020; ASCO Abstract TPS3651
86. Luo J, et al. Cell (2009) PMID: 19490893
87. Barzi et al., 2020; AACR Abstract CT235
88. Van Cutsem E, et al. J. Clin. Oncol. (2011) PMID: 21502544
89. Bokemeyer C, et al. Ann. Oncol. (2011) PMID: 21228335
90. Karapetis CS, et al. N. Engl. J. Med. (2008) PMID: 18946061
91. De Roock W, et al. Ann. Oncol. (2008) PMID: 17998284
92. Douillard JY, et al. Ann. Oncol. (2014) PMID: 24718886
93. Douillard JY, et al. N. Engl. J. Med. (2013) PMID: 24024839
94. Amado RG, et al. J. Clin. Oncol. (2008) PMID: 18316791
95. Lièvre A, et al. Cancer Res. (2006) PMID: 16618717
96. De Roock W, et al. Lancet Oncol. (2011) PMID: 21163703
97. Chen J, et al. BMC Cancer (2014) PMID: 25367198
98. Li W, et al. BMC Cancer (2015) PMID: 25929517
99. Hu J, et al. Medicine (Baltimore) (2016) PMID: 27977612
100. Zekri J, et al. Genet. Mol. Res. (2017) PMID: 28218784
101. Staudacher JJ, et al. Clin Transl Gastroenterol (2017) PMID: 29048416
102. Wang Y, et al. Virchows Arch. (2018) PMID: 29705968
103. Guo F, et al. Sci Rep (2018) PMID: 29666387
104. Mármol I, et al. Int J Mol Sci (2017) PMID: 28106826
105. Kwak MS, et al. Medicine (Baltimore) (2017) PMID: 28858102
106. Kahn S, et al. Anticancer Res. (2017) PMID: 3310850
107. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) PMID: 17150185
108. Bollag G, et al. J. Biol. Chem. (1996) PMID: 8955068
109. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) PMID: 20194776
110. Sci. STKE (2004) PMID: 15367757
111. Eddins S, et al. Cancer Biol. Ther. (2006) PMID: 16969076
112. Feig LA, et al. Mol. Cell. Biol. (1988) PMID: 3043178
113. Gremer L, et al. Hum. Mutat. (2011) PMID: 20949621
114. Janakiraman M, et al. Cancer Res. (2010) PMID: 20570890
115. Kim E, et al. Cancer Discov (2016) PMID: 27147599
116. Lukman S, et al. PLoS Comput. Biol. (2010) PMID: 20838576
117. Naguib A, et al. J Mol Signal (2011) PMID: 21371307
118. Prior IA, et al. Cancer Res. (2012) PMID: 22589270
119. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) PMID: 1565661
120. Scheffek K, et al. Science (1997) PMID: 9219684
121. Scholl C, et al. Cell (2009) PMID: 19490892
122. Smith G, et al. Br. J. Cancer (2010) PMID: 20147967
123. Tyner JW, et al. Blood (2009) PMID: 19075190
124. Valencia A, et al. Biochemistry (1991) PMID: 2029511
125. White Y, et al. Nat Commun (2016) PMID: 26854029
126. Wiest GG, et al. Oncogene (1994) PMID: 8058307
127. Angeles AKJ, et al. Oncol Lett (2019) PMID: 31289513
128. Tong JH, et al. Cancer Biol. Ther. (2014) PMID: 24642870
129. Loree JM, et al. Clin Cancer Res (2021) PMID: 34117033
130. Pentheroudakis G, et al. BMC Cancer (2013) PMID: 23374602
131. Vaughn CP, et al. Genes Chromosomes Cancer (2011) PMID: 21305640
132. Janku F, et al. Target Oncol (2013) PMID: 23400451
133. De Roock W, et al. Lancet Oncol. (2010) PMID: 20619739
134. Irahara N, et al. Diagn. Mol. Pathol. (2010) PMID: 20736745
135. Schirripa M, et al. Int. J. Cancer (2015) PMID: 24806288
136. Cercek A, et al. Clin. Cancer Res. (2017) PMID: 28446505
137. Zhan T, et al. Oncogene (2017) PMID: 27617575
138. Jung YS, et al. Exp Mol Med (2020) PMID: 32037398
139. Krishnamurthy N, et al. Cancer Treat Rev (2018) PMID: 29169144
140. Kawazoe et al., 2021; ESMO Abstract 473P
141. Yamada K, et al. Cancer Res (2021) PMID: 33408116
142. Kanda Y, et al. Biochem Biophys Res Commun (2022) PMID: 34837838
143. Fu Y, et al. Int. J. Cancer (2011) PMID: 21455986
144. Quyn AJ, et al. Surgeon (2008) PMID: 19110823
145. Luke JJ, et al. Clin Cancer Res (2019) PMID: 30635339
146. Logan CY, et al. Annu. Rev. Cell Dev. Biol. (2004) PMID: 15473860
147. Eklof Spink K, et al. EMBO J. (2001) PMID: 11707392
148. Liu J, et al. J. Mol. Biol. (2006) PMID: 16753179
149. Dikovskaya D, et al. J. Cell. Sci. (2010) PMID: 20144988
150. Murphy SJ, et al. Dig. Dis. Sci. (2007) PMID: 17410430

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**APPENDIX**
**References**

151. Aretz S, et al. Hum. Mutat. (2004) PMID: 15459959
152. Landrum MJ, et al. Nucleic Acids Res. (2018) PMID: 29165669
153. Kerr SE, et al. J Mol Diagn (2013) PMID: 23159591
154. Annu Rev Pathol (2011) PMID: 21090969
155. Kastritis E, et al. Int. J. Cancer (2009) PMID: 18844223
156. Half E, et al. Orphanet J Rare Dis (2009) PMID: 19822006
157. Mao JH, et al. Science (2008) PMID: 18787170
158. Yang H, et al. Oncotarget (2015) PMID: 25749036
159. Villaruz LC, et al. Lung Cancer (2014) PMID: 24360397
160. Olson D, et al. Clin Genitourin Cancer (2016) PMID: 27079472
161. Kulkarni et al., 2020; <https://doi.org/10.1016/j.jgyno.2020.05.244>
162. Ng K, et al. Clin. Cancer Res. (2013) PMID: 23743569
163. Ganesan P, et al. Mol. Cancer Ther. (2013) PMID: 24092809
164. Janku F, et al. Cell Rep (2014) PMID: 24440717
165. Wertz IE, et al. Nature (2011) PMID: 21368834
166. Seshagiri S, et al. Nature (2012) PMID: 22895193
167. Brannon AR, et al. Genome Biol. (2014) PMID: 25164765
168. Rajagopalan H, et al. Nature (2004) PMID: 14999283
169. Miyaki M, et al. Oncology (2009) PMID: 19420964
170. Kemp Z, et al. Cancer Res. (2005) PMID: 16357143
171. Grim JE, et al. Mol. Cell. Biol. (2012) PMID: 22473991
172. Iwatsuki M, et al. Int. J. Cancer (2010) PMID: 19739118
173. Welcker M, et al. Nat. Rev. Cancer (2008) PMID: 18094723
174. Akhoondi S, et al. Cancer Res. (2007) PMID: 17909001
175. Welcker M, et al. Genes Dev. (2013) PMID: 24298052
176. Welcker M, et al. Cell Div (2007) PMID: 17298674
177. Strohmaier H, et al. Nature (2001) PMID: 11565034
178. Pashkova N, et al. Mol. Cell (2010) PMID: 21070969
179. O'Neil J, et al. J. Exp. Med. (2007) PMID: 17646409
180. Mal'yukova A, et al. Leukemia (2013) PMID: 23228967
181. Thompson BJ, et al. J. Exp. Med. (2007) PMID: 17646408
182. Horiuchi D, et al. J. Exp. Med. (2012) PMID: 22430491
183. Goga A, et al. Nat. Med. (2007) PMID: 17589519
184. Molenaar JJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) PMID: 19525400
185. Dammert MA, et al. Nat Commun (2019) PMID: 31375684
186. Mollaoglu G, et al. Cancer Cell (2017) PMID: 28089889
187. Cardnell RJ, et al. Oncotarget (2017) PMID: 29088717
188. Wang L, et al. Mol Oncol (2017) PMID: 28417568
189. Takahashi Y, et al. Ann. Oncol. (2015) PMID: 25632068
190. Li Y, et al. Thyroid (2018) PMID: 30226440
191. Mahadevan D, et al. PLoS ONE (2014) PMID: 24893165
192. Park SI, et al. Target Oncol (2019) PMID: 31429028
193. Helfrich BA, et al. Mol. Cancer Ther. (2016) PMID: 27496133
194. Hook KE, et al. Mol. Cancer Ther. (2012) PMID: 22222631
195. Yang D, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) PMID: 20643922
196. He J, et al. Anticancer Drugs (2019) PMID: 30540594
197. Shroff EH, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) PMID: 25964345
198. Effenberger M, et al. Oncotarget (2017) PMID: 29156762
199. Qu X, et al. Biochem. Biophys. Res. Commun. (2018) PMID: 30103944
200. Xiang Y, et al. J. Clin. Invest. (2015) PMID: 25915584
201. Delmore JE, et al. Cell (2011) PMID: 21889194
202. Bandopadhyay P, et al. Clin. Cancer Res. (2014) PMID: 24297863
203. Lovén J, et al. Cell (2013) PMID: 23582323
204. Otto C, et al. Neoplasia (2019) PMID: 31734632
205. Dong LH, et al. J Hematol Oncol (2013) PMID: 23866964
206. Pei Y, et al. Cancer Cell (2016) PMID: 26977882
207. Fu XH, et al. Acta Pharmacol. Sin. (2019) PMID: 30224636
208. Owonikoko TK, et al. J Thorac Oncol (2020) PMID: 31655296
209. Ganesan P, et al. Mol. Cancer Ther. (2014) PMID: 25253784
210. Tannir et al., 2018; ASCO GU Abstract 603
211. Motzer et al., 2019; ESMO Abstract LBA54
212. Pereira CB, et al. PLoS ONE (2013) PMID: 23555992
213. Yasojima H, et al. Eur. J. Cancer (2011) PMID: 21741827
214. Arango D, et al. Cancer Res. (2001) PMID: 11406570
215. Bottone MG, et al. Exp. Cell Res. (2003) PMID: 14516787
216. Cerami E, et al. Cancer Discov (2012) PMID: 22588877
217. Gao J, et al. Sci Signal (2013) PMID: 23550210
218. Tate JG, et al. Nucleic Acids Res. (2019) PMID: 30371878
219. Erisman MD, et al. Mol. Cell. Biol. (1985) PMID: 3837853
220. Erisman MD, et al. Oncogene (1988) PMID: 3283655
221. Wang J, et al. Chin. Med. Sci. J. (1994) PMID: 8086630
222. Herbst A, et al. BMC Genomics (2014) PMID: 24467841
223. Huang MY, et al. Cancer Biomark (2013) PMID: 24240588
224. Toon CW, et al. PLoS ONE (2014) PMID: 24503701
225. Augenlicht LH, et al. Cancer Res. (1997) PMID: 9135021
226. Monnat M, et al. Int. J. Cancer (1987) PMID: 3040597
227. Dang CV, et al. Semin. Cancer Biol. (2006) PMID: 16904903
228. Nesbit CE, et al. Oncogene (1999) PMID: 10378696
229. Blacato J, et al. Br. J. Cancer (2004) PMID: 15083194
230. Fromont G, et al. Hum. Pathol. (2013) PMID: 23574779
231. Ehata S, et al. Cancer Sci. (2007) PMID: 17129361
232. Rausch MP, et al. Anticancer Res. (2009) PMID: 19528470
233. Li YY, et al. Clin. Cancer Res. (2015) PMID: 25589618
234. Fleming NI, et al. Cancer Res. (2013) PMID: 23139211
235. Nature (2014) PMID: 25079317
236. Nature (2012) PMID: 22960745
237. Nature (2014) PMID: 25079552
238. Imielinski M, et al. Cell (2012) PMID: 22980975
239. Uchida K, et al. Cancer Res. (1996) PMID: 8971158
240. Ding L, et al. Nature (2008) PMID: 18948947
241. Boulay JL, et al. Genes Chromosomes Cancer (2001) PMID: 11391794
242. Xie W, et al. Cancer J ( ) PMID: 12967141
243. Kourmoudourou D, et al. Anticancer Res. ( ) PMID: 17695423
244. Xie W, et al. Cancer Res. (2002) PMID: 11809701
245. Liapi G, et al. APMIS (2007) PMID: 17295676
246. Wu SK, et al. World J. Gastroenterol. (2007) PMID: 17729405
247. Macías-Silva M, et al. Cell (1996) PMID: 8980228
248. Xie W, et al. Head Neck (2013) PMID: 22275186
249. Mangone FR, et al. Mol. Cancer (2010) PMID: 20462450
250. Lebrun JJ, et al. Mol. Endocrinol. (1999) PMID: 9892009
251. Lin X, et al. Cell (2006) PMID: 16751101
252. Funaba M, et al. J. Biol. Chem. (2002) PMID: 12193595
253. Massagué J, et al. Genes Dev. (2005) PMID: 16322555
254. Matsuzaki K, et al. Cancer Res. (2009) PMID: 19531654
255. Wu Y, et al. PLoS ONE (2012) PMID: 22539990
256. Hirai H, et al. Cancer Biol. Ther. (2010) PMID: 20107315
257. Bridges KA, et al. Clin. Cancer Res. (2011) PMID: 21799033
258. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) PMID: 21389100
259. Osman AA, et al. Mol. Cancer Ther. (2015) PMID: 25504633
260. Xu L, et al. Mol. Cancer Ther. (2002) PMID: 12489850
261. Xu L, et al. Mol. Med. (2001) PMID: 11713371
262. Camp ER, et al. Cancer Gene Ther. (2013) PMID: 23470564
263. Kim SS, et al. Nanomedicine (2015) PMID: 25240597
264. Pirolo KF, et al. Mol. Ther. (2016) PMID: 27357628
265. Hajdenberg et al., 2012; ASCO Abstract e15010
266. Leijen S, et al. J. Clin. Oncol. (2016) PMID: 27601554
267. Moore E, et al., 2019; ASCO Abstract 5513
268. Leijen S, et al. J. Clin. Oncol. (2016) PMID: 27998224
269. Oza et al., 2015; ASCO Abstract 5506
270. Lee J, et al. Cancer Discov (2019) PMID: 31315834
271. Méndez E, et al. Clin. Cancer Res. (2018) PMID: 29535125
272. Seligmann JF, et al. J Clin Oncol (2021) PMID: 34538072
273. Lehmann S, et al. J. Clin. Oncol. (2012) PMID: 22965953
274. Mohell N, et al. Cell Death Dis (2015) PMID: 26086967
275. Fransson Å, et al. J Ovarian Res (2016) PMID: 27179933
276. Gourley et al., 2016; ASCO Abstract 5571
277. Kwok M, et al. Blood (2016) PMID: 26563132
278. Boudny M, et al. Haematologica (2019) PMID: 30975914
279. Dillon MT, et al. Mol. Cancer Ther. (2017) PMID: 28062704
280. Middleton FK, et al. Cancers (Basel) (2018) PMID: 30127241
281. Goh HS, et al. Cancer Res. (1995) PMID: 7585578
282. Berg M, et al. PLoS ONE (2010) PMID: 21103049
283. Han SW, et al. PLoS ONE (2013) PMID: 23700467
284. Peeters M, et al. Clin. Cancer Res. (2013) PMID: 23325582
285. Malhotra P, et al. Tumour Biol. (2013) PMID: 23526092
286. Di Bartolomeo M, et al. Target Oncol (2014) PMID: 23821376
287. Wangefjord S, et al. Diagn Pathol (2013) PMID: 23337059
288. Russo A, et al. J. Clin. Oncol. (2005) PMID: 16172461
289. Brown CJ, et al. Nat. Rev. Cancer (2009) PMID: 19935675
290. Joerger AC, et al. Annu. Rev. Biochem. (2008) PMID: 18410249
291. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) PMID: 12826609
292. Kamada R, et al. J. Biol. Chem. (2011) PMID: 20978130
293. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) PMID: 28472496
294. Yamada H, et al. Carcinogenesis (2007) PMID: 17690113
295. Bougeard G, et al. J. Clin. Oncol. (2015) PMID: 26014290
296. Sorrell AD, et al. Mol Diagn Ther (2013) PMID: 23355100
297. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) PMID: 11219776
298. Kleihues P, et al. Am. J. Pathol. (1997) PMID: 9006316
299. Gonzalez KD, et al. J. Clin. Oncol. (2009) PMID: 19204208
300. Lalloo F, et al. Lancet (2003) PMID: 12672316
301. Mandelker D, et al. Ann. Oncol. (2019) PMID: 31050713
302. Jaiswal S, et al. N. Engl. J. Med. (2014) PMID: 25426837
303. Genovesse G, et al. N. Engl. J. Med. (2014) PMID: 25426838
304. Xie M, et al. Nat. Med. (2014) PMID: 25326804
305. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) PMID: 28669404
306. Severson EA, et al. Blood (2018) PMID: 29678827
307. Fuster JJ, et al. Circ. Res. (2018) PMID: 29420212

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**References**

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| <p>308. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320</p> <p>309. Chabon JJ, et al. Nature (2020) pmid: 32269342</p> <p>310. Razavi P, et al. Nat. Med. (2019) pmid: 31768066</p> <p>311. Cunningham D, et al. N. Engl. J. Med. (2004) pmid: 15269313</p> | <p>312. Jonker DJ, et al. N. Engl. J. Med. (2007) pmid: 18003960</p> <p>313. Moiseyenko VM, et al. Clin Drug Investig (2018) pmid: 29470838</p> <p>314. Stein et al., 2020; ASCO GI Abstract 96</p> <p>315. Price TJ, et al. Lancet Oncol. (2014) pmid: 24739896</p> <p>316. Sakai D, et al. Eur J Cancer (2020) pmid: 32526634</p> | <p>317. Van Cutsem E, et al. J. Clin. Oncol. (2007) pmid: 17470858</p> <p>318. Pietrantonio F, et al. JAMA Oncol (2019) pmid: 31268481</p> |
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