FOUNDATIONONE®LIQUID CDx

PATIENT
Yang, Ching-Yun

TUMOR TYPE
Unknown primary neuroendocrine tumor (NET)

COUNTRY CODE
TW

REPORT DATE
06 Dec 2021

ORDERED TEST #
ORD-1245817-01

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

## PATIENT

**DISEASE** Unknown primary neuroendocrine tumor (NET)
**NAME** Yang, Ching-Yun
**DATE OF BIRTH** 24 November 1960
**SEX** Female
**MEDICAL RECORD #** 18068821

## PHYSICIAN

**ORDERING PHYSICIAN** Yeh, Yi-Chen
**MEDICAL FACILITY** Taipei Veterans General Hospital
**ADDITIONAL RECIPIENT** None
**MEDICAL FACILITY ID** 205872
**PATHOLOGIST** Not Provided

## SPECIMEN

**SPECIMEN ID** CYY 11/24/1960
**SPECIMEN TYPE** Blood
**DATE OF COLLECTION** 22 November 2021
**SPECIMEN RECEIVED** 26 November 2021

## Biomarker Findings

**Blood Tumor Mutational Burden** - 3 Muts/Mb
**Microsatellite status** - MSI-High Not Detected
**Tumor Fraction** - 23%

## Genomic Findings

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

***KIT*** amplification - equivocal†
***PDGFRA*** amplification - equivocal†
***FGFR3*** amplification - equivocal†
***KEAP1*** S486fs*15
***KDR*** amplification - equivocal†
***TP53*** R213*, splice site 783-2A>C

† See About the Test in appendix for details.

**4** Therapies with Clinical Benefit
**0** Therapies with Resistance
**17** Clinical Trials

| BIOMARKER FINDINGS |
|---|
| **Blood Tumor Mutational Burden -** 3 Muts/Mb |
| **Microsatellite status -** MSI-High Not Detected |
| **Tumor Fraction -** 23% |

| THERAPY AND CLINICAL TRIAL IMPLICATIONS |
|---|
| **No therapies or clinical trials. See Biomarker Findings section** |
| **MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).** |
| **Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.** |

| GENOMIC FINDINGS | | VAF % | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|---|---|
| ***KIT*** - | amplification - equivocal | - | None | Imatinib |
| | | | | Nilotinib |
| | | | | Sorafenib |
| | | | | Sunitinib |
| **10 Trials** see p. 16 | | | | |
| ***PDGFRA*** - | amplification - equivocal | - | None | Imatinib |
| **1 Trial** see p. 18 | | | | |
| ***FGFR3*** - | amplification - equivocal | - | None | None |
| **10 Trials** see p. 13 | | | | |



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| GENOMIC FINDINGS | | VAF % | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|---|---|
| ***KEAP1*** - | S486fs*15 | 25.5% | None | None |
| **1 Trial** see p. 15 | | | | |

## 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.*

***KDR*** - amplification - equivocal ..... p. 9

***TP53*** - R213*, splice site 783-2A>C ..... p. 10

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

Variant Allele Frequency is not applicable for copy number alterations.



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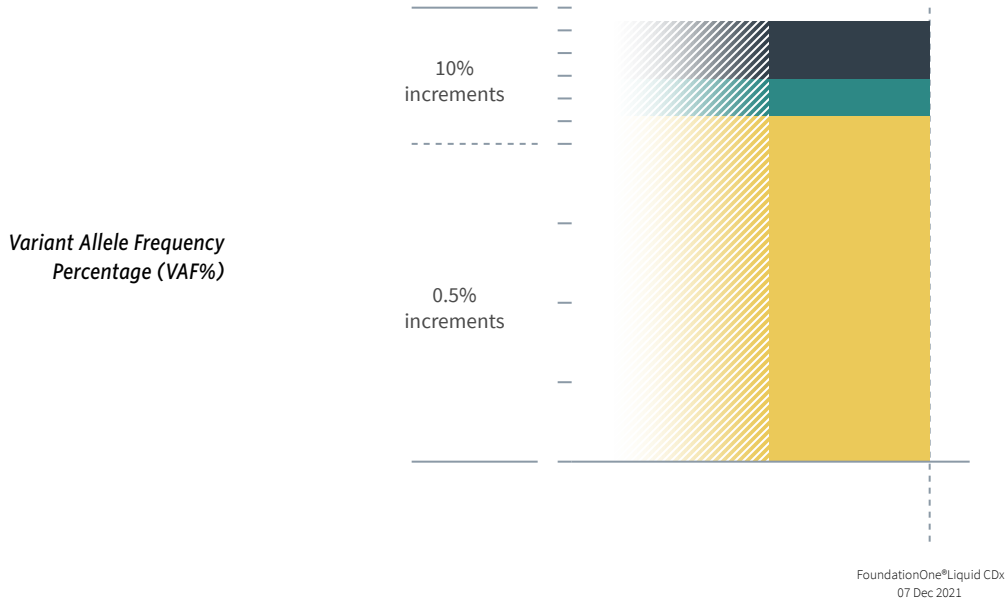


| HISTORIC PATIENT FINDINGS | | ORD-1245817-01 VAF% |
|---|---|---|
| **Blood Tumor Mutational Burden** | | 3 Muts/Mb |
| **Microsatellite status** | | MSI-High Not Detected |
| **Tumor Fraction** | | 23% |
| ***KIT*** | amplification | Detected |
| ***PDGFRA*** | amplification | Detected |
| ***FGFR3*** | amplification | Detected |
| ***KEAP1*** | ● S486fs*15 | 25.5% |
| ***KDR*** | amplification | Detected |
| ***TP53*** | ● splice site 783-2A>C | 16.4% |
| | ● R213* | 14.4% |

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

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

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

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



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an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene
Not Detected = baited but not detected on test
Detected = present (VAF% is not applicable)
VAF% = variant allele frequency percentage
Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status



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BIOMARKER

# Blood Tumor Mutational Burden

**RESULT**
3 Muts/Mb

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

## FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2021)[5-7]. In 1 retrospective study of patients with advanced neuroendocrine tumors not treated with immunotherapy, tumor mutational burden (TMB)-high (≥10 Muts/Mb) was not correlated with any significant difference in OS compared with TMB-low (≤ 10 Muts/Mb) measured in tissue samples (10.4 vs. 6.4 months, adjusted HR = 0.83)[8]. The impact of TMB on the prognosis and clinicopathological features of lung neuroendocrine cancers is unclear; large cell neuroendocrine carcinoma (LCNEC) cases with small cell lung cancer-like molecular features were reported to have significantly higher proliferative activity, as well as a trend toward better clinical benefit from treatment with chemotherapy, than non-small cell lung cancer-like tumors, but the average TMB was not significantly different between the two subsets of LCNEC[9]. MCPyV-negative Merkel cell carcinoma (MCC), associated with higher TMB, has been reported to have a higher number of predicted tumor neoantigens and a significantly higher UV mutation signature than MCPyV-positive MCC[10-11]. Within MCPyV-negative MCC tumors, the mutational burden has been reported to be significantly higher in PD-L1-positive tumors (more than 1% positive tumor and macrophage cells by immunohistochemistry) than in PD-L1-negative tumors[12].

## FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[13-14] and cigarette smoke in lung cancer[15-16], treatment with temozolomide-based chemotherapy in glioma[17-18], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19-23], and microsatellite instability (MSI)[19,22-23]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

# Tumor Fraction

**RESULT**
23%

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results[24]. However, if tumor fraction is not detected as high, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[25-30].

## FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[31]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[32], Ewing sarcoma and osteosarcoma[33], prostate cancer[28], breast cancer[34], leiomyosarcoma[35], esophageal cancer[36], colorectal cancer[37], and gastrointestinal cancer[38].

## FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[39], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[40-41].



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GENE
## *KIT*

**ALTERATION**
amplification - equivocal

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of clinical evidence, primarily in GIST, AML, and systemic mastocytosis, KIT activating alterations are associated with sensitivity to KIT tyrosine kinase inhibitors including imatinib, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, regorafenib, ponatinib, midostaurin, avapritinib, and ripretinib[42-49]. The use of mTOR inhibitors as an alternative therapeutic strategy has demonstrated limited success in KIT-mutated, imatinib-resistant melanoma, with 1 PR and 3 SD observed for 4 patients treated with everolimus[50]. However, no responses were observed for 10 patients with mastocytosis following everolimus monotherapy, with 8/10 patients harboring the KIT D816V mutation[51]. The role of KIT amplification as a biomarker for response to mTOR inhibitors has not been investigated (PubMed, Mar 2021). Clinical benefit has been observed for patients with KIT amplified or overexpressing tumors following treatment with imatinib[52-62], nilotinib[63], sorafenib[64-67], and sunitinib[68-69], suggesting that KIT amplification may be sensitive to these inhibitors. However, evidence demonstrating clinical benefit for regorafenib, dasatinib, pazopanib, or ponatinib in the context of KIT amplified or overexpressing tumors is limited.

### FREQUENCY & PROGNOSIS

KIT alterations were identified in 7% (7/98) of small cell undifferentiated lung cancer cases[70]. KIT protein expression has been reported in 36-83% of SCLC samples[71-73]. KIT protein expression has been observed in 17-77% of lung large cell neuroendocrine cancers[74-78]. KIT activating mutations have been reported in pancreatic neuroendocrine tumors[79]. Published data investigating the prognostic implications of KIT alteration in neuroendocrine tumors are limited (PubMed, Apr 2021).

### FINDING SUMMARY

KIT (also called c-KIT) encodes a cell surface tyrosine kinase receptor that, upon ligand binding and dimerization, activates the PI3K-AKT and RAS-MAPK signaling pathways[80]. KIT aberrations, including point mutations, translocations, amplification, and overexpression, have been associated with various malignancies, and KIT is considered an oncoprotein[81]. KIT has been reported to be amplified in cancer[6] and may be biologically relevant in this context[82-83].

GENE
## *PDGFRA*

**ALTERATION**
amplification - equivocal

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of extensive clinical evidence in solid tumors and hematologic cancers, PDGFRA activating alterations are associated with sensitivity to imatinib[84-121]. Sorafenib has shown clinical and preclinical activity against the FIP1L1-PDGFRA fusion in chronic eosinophilic leukemia (CEL) and mutations associated with clinical resistance to imatinib and sunitinib in both CEL and gastrointestinal stromal tumor (GIST)[122-127]. Complete responses to nilotinib have been reported in patients with CEL or hypereosinophilic syndrome with FIP1L1-PDGFRA or activating mutations[100,128-129]; preclinical evidence has reported efficacy of nilotinib in the context of PDGFRA mutations associated with GIST[130-131]. Patients with GIST harboring PDGFRA activating mutations have been reported to derive clinical benefit from treatment with sunitinib[132] or regorafenib[133-134]. Preclinical studies have reported sensitivity of activating PDGFRA mutations and FIP1L1-PDGFRA fusion to dasatinib[124,130]. PDGFRA D842 mutations were reported to be sensitive to avapritinib in clinical[42] and preclinical[42] studies of GIST, and demonstrated sensitivity to ripretinib for 1 patient[135].

### FREQUENCY & PROGNOSIS

PDGFRA amplification in the context of neuroendocrine carcinoma has not been an area of significant study in the scientific literature (PubMed, May 2021). Expression of PDGFR-alpha has been reported in 15%-100% of gastrointestinal neuroendocrine tumors analyzed[136-139]. In one study, high expression of PDGFR-alpha was reported in 33% of gastroenteropancreatic neuroendocrine tumors and was associated with decreased disease-specific survival[79].

### FINDING SUMMARY

PDGFRA encodes platelet-derived growth factor receptor alpha (PDGFR-alpha), a tyrosine kinase receptor that, upon binding of cognate ligands (PDGFA or PDGFB), activates several signaling pathways, including PI3K and MAPK[140]. PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies[81]. Amplification of PDGFRA, frequently occurring with amplification of the genes KDR and KIT, has been associated with increased PDGFRA expression[141-144] and poor prognosis[141,145-147] in some subtypes of glioma.



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GENE
## *FGFR3*

**ALTERATION**
amplification - equivocal

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Alterations that activate FGFR3 may predict sensitivity to selective FGFR kinase inhibitors, including erdafitinib[148-150], pemigatinib[151], infigratinib[152-153], rogaratinib[154], Debio 1347[155-156], and derazantinib[157]; multikinase inhibitors such as pazopanib[158-159] and ponatinib[160-161]; and vofatamab, an antibody targeting FGFR3[162-164] . In the context of FGFR3 alterations, FGFR inhibitors, such as erdafitinib[148], pemigatinib[151], infigratinib[152], rogaratinib[154], and Debio 1347[165], have predominantly been studied in the context of urothelial carcinoma, resulting in ORRs of 25-40% and DCRs of 64-80%. Clinical benefit has been reported in patients with gliomas harboring FGFR3 fusions treated in a Phase 1 trial of erdafitinib[149,166], and a prolonged SD has been observed in a case study treated with Debio 1347[167]. For infigratinib, activity against non-urothelial tumors harboring FGFR3 alterations are limited[168], with responses reported in individuals with an FGFR3-amplified and -rearranged glioma or FGFR3-mutated head and neck squamous cell carcinoma with co-occurring FGF amplifications[169].

### FREQUENCY & PROGNOSIS

The frequency of FGFR3 amplification in neuroendocrine tumors has not been evaluated (cBioPortal, PubMed, Jan 2021)[5-6]. Published data investigating the prognostic implications of FGFR3 alteration in neuroendocrine tumors are limited (PubMed, Jan 2021).

### FINDING SUMMARY

FGFR3 (Fibroblast growth factor receptor 3) encodes a receptor tyrosine kinase that typically promotes cell cycle progression and angiogenesis via activation of downstream signaling pathways, including RAS-MAPK and AKT; gain of function mutations in FGFRs have been reported in several cancer types[170-172]. FGFR3 has been reported to be amplified in cancer[6] and may be biologically relevant in this context[82-83].



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GENE
# *KEAP1*

**ALTERATION**
S486fs*15

**TRANSCRIPT ID**
NM_012289

**CODING SEQUENCE EFFECT**
1455_1456insAT

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

A study of patients with localized non-small cell lung cancer (NSCLC) identified pathogenic KEAP1 and NFE2L2 mutations as predictors of local recurrence following radiotherapy but not surgery; limited preclinical data also showed that treatment with a glutaminase inhibitor sensitized KEAP1-mutated NSCLC cells to radiation[173]. In other preclinical studies, treatment with AKT inhibitors sensitized lung cancer cells harboring KEAP1 or NFE2L2 mutations to both chemotherapy and radiation therapy[174-175]. Mixed clinical data have been reported for the association between KEAP1 mutations and the response to immunotherapy. A pan-cancer study of immunotherapy showed that patients with KEAP1 mutations had shorter OS (10 vs. 20 months) than those without[176]. However, another study across solid tumors showed that KEAP1 mutations were associated with higher tumor mutational burden (TMB) and PD-L1 expression, as well as improved survival outcomes with immunotherapy compared with other treatments (20.0 vs. 11.5 months)[177]. For patients with non-small cell lung cancer (NSCLC), a study of PD-L1 inhibitors showed that patients with concurrent mutations of STK11 and KEAP1 (n=39) experienced significantly shorter PFS (1.6 vs. 2.5 months, HR=1.5) and OS (4 vs. 11 months, HR=1.9) compared with patients with STK11- and KEAP1-wildtype tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 Muts/Mb)[178]. Retrospective analyses of patients with NSCLC who received immunotherapy reported reduced OS (p=0.040) for patients harboring KEAP1- or NFE2L2-mutated tumors[179] or STK11- or KEAP1-mutated tumors (p <0.001)[180] compared with those without. Studies of immune checkpoint inhibitors for patients with lung adenocarcinoma showed that coexisting mutations between KEAP1, PBRM1, SMARCA4, STK11, and KRAS were associated with worse OS[181]. An exploratory analysis of a subset of patients with PD-L1-positive NSCLC treated in the first-line setting with pembrolizumab showed similar ORR, PFS, and OS when comparing patients with STK11 or KEAP1 mutations and those without[182]. In addition, preclinical data suggest that KEAP1 inactivation increases tumor demand for glutamine and increases tumor sensitivity to glutaminase inhibitors like telaglenastat[183-185]. Limited clinical data suggest that KEAP1 mutations may predict improved clinical benefit from combinations of glutaminase inhibitors and anti-PD-1 inhibitors[186]; a Phase 1/2 study of the glutaminase inhibitor telaglenastat (CB-839) plus nivolumab to treat advanced NSCLC reported better clinical benefit rates and median PFS for patients with KEAP1 mutations (75% [3/4] vs. 15% [2/13], 6.4 vs. 3.7 months), KRAS mutations (38% [3/8] vs. 20% [2/10], 4.5 vs. 3.7 months), or KEAP1 and KRAS concurrent mutations (100% [2/2] vs. 13% [1/8], 7.2 vs. 3.7 months) compared with patients without these mutations[186]. The KEAP1 mutation has also been identified as a potential biomarker for sensitivity to combined AKT and TXNRD1 inhibition in lung cancer[187].

## FREQUENCY & PROGNOSIS

Somatic mutation of KEAP1 occurs in a range of solid tumors, including gastric, hepatocellular, colorectal, and lung cancers[188]. KEAP1 mutations are rare in hematological malignancies, occurring in fewer than 1% of samples analyzed (COSMIC, 2021)[7]. In a retrospective analysis of the pan-solid MSKCC dataset, KEAP1 mutation correlated with reduced OS (13.28 vs. 26.53 months)[177].

## FINDING SUMMARY

KEAP1 encodes a substrate adaptor protein that regulates the cellular response to oxidative stress by providing substrate specificity for a CUL3-dependent ubiquitin ligase[189]. KEAP1 exerts anti-tumor effects through negative regulation of NRF2, a transcription factor encoded by NFE2L2[190-192]; KEAP1 inactivation promotes cancer progression through NRF2-mediated chemoresistance and cell growth[191-192].



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GENE
## *KDR*

ALTERATION
amplification - equivocal

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of clinical benefit for patients with ccRCC[193-197] and a patient with breast angiosarcoma[198], high VEGFR-2 expression has been associated with sensitivity to sunitinib. However, because data supporting concordance between VEGFR-2 expression and KDR genomic biomarkers are limited, it is unclear whether these therapeutic strategies would be beneficial in this case. On the basis of extensive clinical evidence across multiple tumor types, expression of plasma or tumor VEGFR-1 or VEGFR-2 has not been established as a reliable biomarker to predict response to the VEGFA-targeted agent bevacizumab[199-218].

### FREQUENCY & PROGNOSIS

KDR mutation has been reported in 4.9% of lung small cell carcinoma, 4.8% of pancreatic carcinoid-endocrine tumor, 5.0% (3/60) of lung large cell carcinoma, and 2.3% of lung carcinoid-endocrine tumor samples analyzed in COSMIC, but was not detected in analyzed small cell carcinoma of the cervix, ovary, or urinary tract or carcinoid-endocrine tumors of the large intestine (COSMIC, Apr 2021)[7]. A study of pulmonary carcinoids and neuroendocrine carcinomas found an inverse correlation of KDR expression and tumor malignancy[219]. Increased expression of KDR has been detected in various types of neuroendocrine tumors, including lung neuroendocrine cell hyperplasias and pancreatic endocrine tumors[220-224]. Published data investigating the prognostic implications of KDR alterations in neuroendocrine or carcinoid carcinomas are limited (PubMed, May 2021).

### FINDING SUMMARY

KDR encodes vascular endothelial growth factor receptor 2 (VEGFR2), a member of the vascular endothelial growth factor receptor (VEGFR) family. It is a receptor tyrosine kinase that transmits signals from VEGFA and is involved in both tumor angiogenesis and vasculogenesis during development[225]. KDR amplification has been reported in many tumor types and may be oncogenic[225].



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

GENE
# *TP53*

**ALTERATION**
R213*, splice site 783-2A>C

**TRANSCRIPT ID**
NM_000546, NM_000546

**CODING SEQUENCE EFFECT**
637C>T, 783-2A>C

## 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[226-229], or p53 gene therapy and immunotherapeutics such as SGT-53[230-234] and ALT-801[235]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[236]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[237]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[238]. 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[239]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[240]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[241]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[234]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[242]. 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[243-244]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[245-246]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

## FREQUENCY & PROGNOSIS

TP53 mutation has been reported in a number of carcinoid-endocrine cases, including 52% (15/29) of stomach, 10% of large intestine, 4% of lung, 7% of pancreatic, and 3% of small intestine origin; TP53 mutations were also observed in 19% of Merkel cell carcinomas, 60–71% (6/10–5/7) of prostate small cell carcinomas, 47% of cervical endocrine tumors, and 70% of small cell lung cancers (SCLCs) (COSMIC, Jan 2021)[7,247-254]. High p53 expression has been reported to be associated with poor prognosis in gastric neuroendocrine and gastroenteropancreatic neuroendocrine tumors[255-256]. The frequency of TP53 mutation or loss and altered p53 levels in neuroendocrine lung tumors has been correlated with the degree of malignancy, as TP53 alterations are more frequent in the most malignant tumor types, including SCLC and large cell neuroendocrine carcinoma[257-259].

## FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[260]. Alterations such as seen here may disrupt TP53 function or expression[261-265].

## POTENTIAL DIAGNOSTIC IMPLICATIONS

Mutations in TP53 or RB1 are characteristic of poorly differentiated neuroendocrine carcinomas (NECs) (NCCN Neuroendocrine and Adrenal Tumors, v1.2021)[266-269].

## 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)[270]. 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[271-273], including sarcomas[274-275]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[276] to 1:20,000[275]. 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[277]. 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[278-283]. 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[278-279]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[284]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[282,285-286]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.



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## Imatinib

*Assay findings association*

**KIT**
amplification - equivocal

**PDGFRA**
amplification - equivocal

### AREAS OF THERAPEUTIC USE

Imatinib targets the BCR-ABL fusion protein, PDGFR, and KIT. It is FDA approved for the treatment of KIT-positive gastrointestinal stromal tumors (GIST), Ph+ chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL), myelodysplastic syndrome/ myeloproliferative syndrome (MDS/MPS), aggressive systemic mastocytosis without a D816V KIT mutation, hypereosinophilic syndrome and/or chronic eosinophilic leukemia, and dermatofibrosarcoma protuberans. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[53-54,96,287] , KIT-amplified[52-55] , or KIT-expressing tumors[57-62,288-289] , KIT activating alterations may confer sensitivity to imatinib. PDGFRA amplification may predict sensitivity to tyrosine kinase inhibitors such as imatinib; a patient with Merkel cell carcinoma expressing PDGFRA achieved a complete response to imatinib[94].

### SUPPORTING DATA

A Phase 2 trial of imatinib in Merkel cell carcinoma (MCC) reported 1 partial response (4%) with median progression free survival of 1 month and median overall survival of 5 months[290]. Three additional cases of imatinib monotherapy benefiting patients with MCC, including a 20+ month ongoing complete response by a patient with a PDGFR expression[94] and a 6+ month response by a patient with KIT expression[291] have been reported[94,291-292] . A Phase 2 study of 68 patients with small cell lung cancer (SCLC) treated with imatinib in combination with chemotherapy reported an objective response rate of 66% and a median overall survival of 8.4 months[293]. Other studies of SCLC treated with imatinib as a single agent did not report any clinical benefit[294-295] . A Phase 2 study of imatinib in patients with carcinoid tumors has reported partial response and stable disease in 4% (2/27) and 63% (17/27) of patients, respectively[296].

## Nilotinib

*Assay findings association*

**KIT**
amplification - equivocal

### AREAS OF THERAPEUTIC USE

Nilotinib targets tyrosine kinases such as ABL (including BCR-ABL), PDGFRs, KIT, CSF1R, DDR1, and DDR2. It is FDA approved to treat newly diagnosed pediatric or adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, adults with Ph+ CML in chronic or accelerated phase with resistance or intolerance to prior therapy including imatinib, and pediatric patients with Ph+ CML in chronic phase with resistance or intolerance to prior tyrosine-kinase inhibitor therapy. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[63,297-300] , KIT-amplified[63], or KIT-expressing tumors[301], KIT activating alterations may confer sensitivity to nilotinib.

### SUPPORTING DATA

Clinical data on the efficacy of nilotinib for the treatment of neuroendocrine tumors or small cell carcinomas are limited (PubMed, Dec 2021). Nilotinib has been primarily investigated as a therapeutic option for the treatment of CML or gastrointestinal stromal tumors (GIST). In the context of CML, a Phase 3 clinical trial of Ph+ patients treated with imatinib or nilotinib (300 mg or 400 mg) reported progression-free survival (PFS) rates of 93% and 97-98% and overall survival (OS) rates of 93% and 94-97%, respectively, at 4 years[302]. For imatinib-resistant Japanese patients with CML, a Phase 2 trial reported a 47.8% major medical response rate to treatment with nilotinib at 12 months[303]. A Phase 3 clinical trial of single-agent nilotinib in 240 patients with advanced GIST who failed prior treatment with imatinib or sunitinib reported no significant difference in progression-free survival between nilotinib and the best supportive care, but did report increased overall survival for nilotinib-treated patients[304]. A Phase 2 trial has shown that nilotinib was well tolerated and suggested it may be particularly useful for treating patients with GIST harboring mutations in KIT exon 17[305]. Preclinical, cell-based assays have reported efficacy for nilotinib alone and in combination with additional therapies in the context of leiomyosarcoma and synovial sarcoma[306].

## Sorafenib

*Assay findings association*

**KIT**
amplification - equivocal

### AREAS OF THERAPEUTIC USE

Sorafenib is a kinase inhibitor that targets the RAF kinases, KIT, FLT3, RET, VEGFRs, and PDGFRs. It is FDA approved for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and recurrent or metastatic differentiated thyroid carcinoma. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[307-314] or KIT-expressing tumors[64-67] , KIT activating alterations may predict sensitivity to sorafenib.

### SUPPORTING DATA

In a Phase 1 study of sorafenib with everolimus in patients with advanced neuroendocrine tumors (NETs), 62% of patients had some degree of tumor shrinkage, and a partial response was observed in one patient and stable disease in 13 patients, while three patients progressed[315]. A Phase 2 study of 44 NET patients treated with a combination therapy of sorafenib and bevacizumab, reported a median progression free survival (PFS) of 12.4 months; however, there was high number of adverse events with this combination therapy[316]. In one case report, sorafenib was effective in a patient with a pancreatic endocrine tumor, eliciting progression-free survival (PFS) for longer than 13 months[317]. Another case study of a single patient with paraganglioma treated with sorafenib reported promising results[318]. In another clinical study, 1/22 patients with advanced neuroendocrine tumors experienced a partial response (PR) to sorafenib[319]. A Phase 2 study of bevacizumab in combination with sorafenib in patients with advanced neuroendocrine tumors (NETs) reported enhanced clinical benefit from the combination, with an objective response rate of 9.4% and a median progression-free survival (PFS) of 12.4 months, but increased toxicity compared with either drug administered as a monotherapy[316]. A Phase 1 trial of sorafenib in combination with everolimus in patients with NETs reported tumor shrinkage in 62% of patients, with 1 PR, 13 stable diseases (SD), and 3 progressive diseases (PD), but with increased toxicity over either agent alone[315].

## Sunitinib

*Assay findings association*

**KIT**
amplification - equivocal

### AREAS OF THERAPEUTIC USE

Sunitinib is a small-molecule tyrosine kinase inhibitor that targets PDGFRs, VEGFRs, KIT, FLT3, CSF-1R, and RET. It is FDA approved for the treatment of advanced or metastatic pancreatic neuroendocrine tumors, gastrointestinal stromal tumors (GISTs) in patients who have progressed on or are intolerant to imatinib, and advanced renal cell carcinoma (RCC) as well as for the adjuvant treatment of patients at high risk of recurrent RCC after nephrectomy. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[68,320-324] or KIT-expressing tumors[68-69] , KIT activating alterations may predict sensitivity to sunitinib.

### SUPPORTING DATA

In a Phase 3 trial for patients with advanced pancreatic neuroendocrine tumors (pNET), sunitinib treatment improved median PFS (11.4 vs. 5.5 months) and ORR (9% vs. 0%) as compared to placebo[325]; no significant difference in median OS was observed between the treatment groups in a 5-year follow up study[326]. A Phase 2 trial comparing sunitinib treatment for patients with advanced neuroendocrine tumors reported improved ORR (17% [11/66] vs. 2% [1/41]) for patients with pNET as compared to those with non-pancreatic carcinoid tumors (including lung, stomach, and colon)[327].

**NOTE** Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.



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**IMPORTANT** Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

**GENE**
## *FGFR3*

**RATIONALE**
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR3.

**ALTERATION**
amplification - equivocal

### NCT04803318

**PHASE 2**

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

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

**LOCATIONS:** Guangzhou (China)

### NCT03564691

**PHASE 1**

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

**TARGETS**
ITL4, FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

**LOCATIONS:** Seoul (Korea, Republic of), Tokyo (Japan), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington

### NCT04008797

**PHASE 1**

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

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

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

### NCT04042116

**PHASE 1/2**

A Study to Evaluate Lucitanib in Combination With Nivolumab in Patients With a Solid Tumor

**TARGETS**
FGFRs, VEGFRs, PD-1

**LOCATIONS:** Innsbruck (Austria), Essen (Germany), Bologna (Italy), Naples (Italy), Leuven (Belgium), Brussels (Belgium), Ghent (Belgium), Washington, Barcelona (Spain), Madrid (Spain)

### NCT04565275

**PHASE 1/2**

A Study of ICP-192 in Patients With Advanced Solid Tumors

**TARGETS**
FGFR1, FGFR2, FGFR3, FGFR4

**LOCATIONS:** Colorado, Minnesota, Arizona, Florida



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## NCT02272998

**PHASE 2**

Ponatinib for Patients Whose Advanced Solid Tumor Cancer Has Activating Mutations Involving the Following Genes: FGFR1, FGFR2, FGFR3, FGFR4, RET, KIT.

**TARGETS**
ABL, FGFRs, FLT3, KIT, RET, VEGFRs

**LOCATIONS:** Ohio

## NCT04729348

**PHASE 2**

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

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

**LOCATIONS:** Massachusetts

## NCT03950609

**PHASE 2**

Lenvatinib and Everolimus in Treating Patients With Advanced, Unresectable Carcinoid Tumors

**TARGETS**
FGFRs, KIT, PDGFRA, RET, VEGFRs, mTOR

**LOCATIONS:** Texas

## NCT03290079

**PHASE 2**

Phase II Study of Pembrolizumab and Lenvatinib in Advanced Well-differentiated Neuroendocrine Tumors

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

**LOCATIONS:** Florida

## NCT02856425

**PHASE 1**

Trial Of Pembrolizumab And Nintedanib

**TARGETS**
FGFR1, FGFR2, FGFR3, FLT3, LCK, LYN, SRC, VEGFRs, PD-1

**LOCATIONS:** Villejuif (France)

**GENE**
*KEAP1*

**ALTERATION**
S486fs*15

**RATIONALE**
KEAP1 inactivation may predict sensitivity to glutaminase inhibitors.

## NCT03872427

**PHASE 2**

Testing Whether Cancers With Specific Mutations Respond Better to Glutaminase Inhibitor, CB-839 HCl, Anti-Cancer Treatment, BeGIN Study

**TARGETS**
GLS

**LOCATIONS:** Kansas, Missouri, Illinois



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**GENE**
*KIT*

**ALTERATION**
amplification - equivocal

**RATIONALE**
KIT amplification or activating mutations may predict sensitivity to small molecule tyrosine kinase inhibitors. Also, because KIT activation leads to activation of the PI3K-AKT-mTOR pathway, PI3K and mTOR pathway inhibitors may be relevant in a tumor with KIT activation.

## NCT04337463

**PHASE NULL**

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

**TARGETS**
mTORC1, mTORC2, PD-1

**LOCATIONS:** Chongqing (China), Chengdu (China)

## NCT04803318

**PHASE 2**

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

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

**LOCATIONS:** Guangzhou (China)

## NCT02461849

**PHASE 2**

Patients With Refractory, Metastatic Cancer Harboring KIT Mutation or Amplification to Investigate the Clinical Efficacy and Safety of Imatinib Therapy

**TARGETS**
KIT, ABL

**LOCATIONS:** Seoul (Korea, Republic of)

## NCT03564691

**PHASE 1**

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

**TARGETS**
ITL4, FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

**LOCATIONS:** Seoul (Korea, Republic of), Tokyo (Japan), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington

## NCT04008797

**PHASE 1**

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

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

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



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## NCT03297606

**PHASE 2**

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

## NCT04729348

**PHASE 2**

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

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

**LOCATIONS:** Massachusetts

## NCT03711058

**PHASE 1/2**

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

**TARGETS**
PD-1, PI3K

**LOCATIONS:** Maryland

## NCT04449549

**PHASE 2**

Rapid Analysis and Response Evaluation of Combination Anti-Neoplastic Agents in Rare Tumors (RARE CANCER) Trial: RARE 1 Nilotinib and Paclitaxel

**TARGETS**
ABL, KIT

**LOCATIONS:** Maryland

## NCT03950609

**PHASE 2**

Lenvatinib and Everolimus in Treating Patients With Advanced, Unresectable Carcinoid Tumors

**TARGETS**
FGFRs, KIT, PDGFRA, RET, VEGFRs, mTOR

**LOCATIONS:** Texas

**GENE**
*PDGFRA*

**RATIONALE**
PDGFRA amplification may predict sensitivity to imatinib and to anti-PDGFRA antibodies.

**ALTERATION**
amplification - equivocal

| **NCT01738139** | **PHASE 1** |
|---|---|
| Ipilimumab and Imatinib Mesylate in Advanced Cancer | **TARGETS** KIT, ABL, CTLA-4 |

**LOCATIONS:** Texas



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**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.

***IRS2***
A512T

***MST1R***
R504C

***NOTCH3***
C654F

***RB1***
K154del

***ROS1***
D2108G

***WHSC1 (MMSET)***
amplification



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## APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ***ABL1*** **Exons 4-9** | *ACVR1B* | ***AKT1*** **Exon 3** | *AKT2* | *AKT3* | ***ALK*** **Exons 20-29, Introns 18, 19** | *ALOX12B* | *AMER1* (FAM123B) | ***APC*** |
| ***AR*** | ***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16** | *ARFRP1* | *ARID1A* | *ASXL1* | ***ATM*** | ***ATR*** | *ATRX* | *AURKA* |
| *AURKB* | *AXIN1* | *AXL* | *BAP1* | *BARD1* | *BCL2* | *BCL2L1* | *BCL2L2* | *BCL6* |
| *BCOR* | *BCORL1* | *BCR** Introns 8, 13, 14 | ***BRAF*** **Exons 11-18,** Introns 7-10 | ***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20 | ***BRCA2*** Intron 2 | *BRD4* | *BRIP1* | *BTG1* |
| *BTG2* | ***BTK*** **Exons 2, 15** | *C11orf30* (EMSY) | *C17orf39* (GID4) | *CALR* | *CARD11* | *CASP8* | *CBFB* | *CBL* |
| ***CCND1*** | *CCND2* | *CCND3* | *CCNE1* | *CD22* | *CD70* | *CD74** Introns 6-8 | *CD79A* | *CD79B* |
| ***CD274*** **(PD-L1)** | *CDC73* | ***CDH1*** | ***CDK12*** | ***CDK4*** | ***CDK6*** | *CDK8* | *CDKN1A* | *CDKN1B* |
| ***CDKN2A*** | *CDKN2B* | *CDKN2C* | *CEBPA* | *CHEK1* | ***CHEK2*** | *CIC* | *CREBBP* | ***CRKL*** |
| *CSF1R* | *CSF3R* | *CTCF* | *CTNNA1* | ***CTNNB1*** **Exon 3** | *CUL3* | *CUL4A* | *CXCR4* | *CYP17A1* |
| *DAXX* | *DDR1* | ***DDR2*** **Exons 5, 17, 18** | *DIS3* | *DNMT3A* | *DOT1L* | *EED* | ***EGFR*** **Introns 7,** 15**, 24-27** | *EP300* |
| *EPHA3* | *EPHB1* | *EPHB4* | ***ERBB2*** | ***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25** | *ERBB4* | *ERCC4* | *ERG* | ***ERRFI1*** |
| ***ESR1*** **Exons 4-8** | *ETV4** Intron 8 | *ETV5** Introns 6, 7 | ***ETV6**** **Introns 5, 6** | *EWSR1** Introns 7-13 | ***EZH2*** **Exons 4, 16, 17, 18** | *EZR** Introns 9-11 | *FAM46C* | *FANCA* |
| *FANCC* | *FANCG* | *FANCL* | *FAS* | *FBXW7* | *FGF10* | *FGF12* | *FGF14* | *FGF19* |
| *FGF23* | *FGF3* | *FGF4* | *FGF6* | ***FGFR1*** Introns 1, 5, **Intron 17** | ***FGFR2*** Intron 1, **Intron 17** | ***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17** | *FGFR4* | *FH* |
| *FLCN* | *FLT1* | ***FLT3*** **Exons 14, 15, 20** | ***FOXL2*** | *FUBP1* | *GABRA6* | *GATA3* | *GATA4* | *GATA6* |
| ***GNA11*** **Exons 4, 5** | *GNA13* | ***GNAQ*** **Exons 4, 5** | ***GNAS*** **Exons 1, 8** | *GRM3* | *GSK3B* | *H3F3A* | *HDAC1* | *HGF* |
| *HNF1A* | ***HRAS*** **Exons 2, 3** | *HSD3B1* | *ID3* | ***IDH1*** **Exon 4** | ***IDH2*** **Exon 4** | *IGF1R* | *IKBKE* | *IKZF1* |
| *INPP4B* | *IRF2* | *IRF4* | *IRS2* | *JAK1* | ***JAK2*** **Exon 14** | ***JAK3*** **Exons 5, 11, 12, 13, 15, 16** | *JUN* | *KDM5A* |
| *KDM5C* | *KDM6A* | *KDR* | *KEAP1* | *KEL* | ***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16 | *KLHL6* | *KMT2A* (MLL) Introns 6, 8-11, Intron 7 | *KMT2D* (MLL2) |



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## APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ***KRAS*** | *LTK* | *LYN* | *MAF* | ***MAP2K1*** **(MEK1) Exons 2, 3** | ***MAP2K2*** **(MEK2) Exons 2-4, 6, 7** | *MAP2K4* | *MAP3K1* | *MAP3K13* |
| *MAPK1* | *MCL1* | ***MDM2*** | *MDM4* | *MED12* | *MEF2B* | *MEN1* | *MERTK* | ***MET*** |
| *MITF* | *MKNK1* | *MLH1* | ***MPL*** **Exon 10** | *MRE11A* | *MSH2* Intron 5 | *MSH3* | *MSH6* | *MST1R* |
| *MTAP* | ***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56** | *MUTYH* | *MYB** Intron 14 | ***MYC*** **Intron 1** | *MYCL* (MYCL1) | ***MYCN*** | ***MYD88*** **Exon 4** | *NBN* |
| ***NF1*** | *NF2* | *NFE2L2* | *NFKBIA* | *NKX2-1* | *NOTCH1* | *NOTCH2* Intron 26 | *NOTCH3* | ***NPM1*** **Exons 4-6, 8, 10** |
| ***NRAS*** **Exons 2, 3** | *NSD3* (WHSC1L1) | *NT5C2* | ***NTRK1*** **Exons 14, 15, Introns 8-11** | *NTRK2* Intron 12 | ***NTRK3*** **Exons 16, 17** | *NUTM1** Intron 1 | *P2RY8* | ***PALB2*** |
| *PARK2* | *PARP1* | *PARP2* | *PARP3* | *PAX5* | *PBRM1* | *PDCD1* (PD-1) | ***PDCD1LG2*** **(PD-L2)** | ***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11** |
| ***PDGFRB*** **Exons 12-21, 23** | *PDK1* | *PIK3C2B* | *PIK3C2G* | ***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)** | *PIK3CB* | *PIK3R1* | *PIM1* | *PMS2* |
| *POLD1* | *POLE* | *PPARG* | *PPP2R1A* | *PPP2R2A* | *PRDM1* | *PRKAR1A* | *PRKCI* | *PTCH1* |
| ***PTEN*** | ***PTPN11*** | *PTPRO* | *QKI* | *RAC1* | *RAD21* | *RAD51* | *RAD51B* | *RAD51C* |
| *RAD51D* | *RAD52* | *RAD54L* | ***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8 | *RARA* Intron 2 | ***RB1*** | *RBM10* | *REL* | ***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11** |
| *RICTOR* | *RNF43* | ***ROS1*** **Exons 31, 36-38, 40, Introns 31-35** | *RPTOR* | *RSPO2** Intron 1 | *SDC4** Intron 2 | *SDHA* | *SDHB* | *SDHC* |
| *SDHD* | *SETD2* | *SF3B1* | *SGK1* | *SLC34A2** Intron 4 | *SMAD2* | *SMAD4* | *SMARCA4* | *SMARCB1* |
| ***SMO*** | *SNCAIP* | *SOCS1* | *SOX2* | *SOX9* | *SPEN* | *SPOP* | *SRC* | *STAG2* |
| *STAT3* | ***STK11*** | *SUFU* | *SYK* | *TBX3* | *TEK* | *TERC** ncRNA | ***TERT**** **Promoter** | *TET2* |
| *TGFBR2* | *TIPARP* | *TMPRSS2** Introns 1-3 | *TNFAIP3* | *TNFRSF14* | ***TP53*** | *TSC1* | *TSC2* | *TYRO3* |
| *U2AF1* | ***VEGFA*** | *VHL* | *WHSC1* | *WT1* | *XPO1* | *XRCC2* | *ZNF217* | *ZNF703* |

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

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction



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FoundationOne Liquid CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

## ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

## INTENDED USE

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

## TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

## THE REPORT

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

## QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

## RANKING OF THERAPIES AND CLINICAL TRIALS

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

*Ranking of Clinical Trials*
Pediatric trial qualification → Geographical proximity → Later trial phase.

## LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from observed aneuploid instability in the sample.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.
11. Alterations reported may include somatic (not

inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.

12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

## VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

## VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

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

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). 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. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

## LEVEL OF EVIDENCE NOT PROVIDED

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

## NO GUARANTEE OF CLINICAL BENEFIT

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

## NO GUARANTEE OF REIMBURSEMENT

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

## TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

## SELECT ABBREVIATIONS

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

MR Suite Version 5.1.1



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1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
4. Li et al., 2020; ASCO Abstract 6511
5. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
6. Gao J, et al. Sci Signal (2013) pmid: 23550210
7. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
8. Shao C, et al. JAMA Netw Open (2020) pmid: 33119110
9. Rekhtman N, et al. Clin. Cancer Res. (2016) pmid: 26960398
10. Harms PW, et al. Cancer Res. (2015) pmid: 26238782
11. Goh G, et al. Oncotarget (2016) pmid: 26655088
12. Wong SQ, et al. Cancer Res. (2015) pmid: 26627015
13. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
14. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
15. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
16. Rizvi NA, et al. Science (2015) pmid: 25765070
17. Johnson BE, et al. Science (2014) pmid: 24336570
18. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
19. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
20. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
21. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
22. Nature (2012) pmid: 22810696
23. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
24. Li et al., 2021; AACR Abstract 2231
25. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
26. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
27. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
28. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
29. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
30. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
31. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
32. Lapin M, et al. J Transl Med (2018) pmid: 30400802
33. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
34. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
35. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
36. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
37. Fan G, et al. PLoS ONE (2017) pmid: 28187169
38. Vu et al., 2020; DOI: 10.1200/PO.19.00204
39. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
40. Zhang EW, et al. Cancer (2020) pmid: 32757294
41. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
42. Evans EK, et al. Sci Transl Med (2017) pmid: 29093181
43. Abbaspour Babaei M, et al. Drug Des Devel Ther (2016) pmid: 27536065
44. Ramaswamy A, et al. J Gastrointest Oncol (2016) pmid: 27563456
45. Demetri GD, et al. Lancet (2013) pmid: 23177515
46. Gotlib J, et al. N. Engl. J. Med. (2016) pmid: 27355533
47. Jawhar M, et al. Blood (2017) pmid: 28424161
48. Xu X, et al. Int J Clin Exp Pathol (2014) pmid: 25031773
49. Gotlib J, et al. Blood (2005) pmid: 15972446
50. Si L, et al. J. Clin. Oncol. (2012) pmid: 22162580
51. Parikh SA, et al. Leuk Lymphoma (2010) pmid: 20038218
52. Wei X, et al. Oncol. Res. (2019) pmid: 30075827
53. Hodi FS, et al. J. Clin. Oncol. (2013) pmid: 23775962
54. Carvajal RD, et al. JAMA (2011) pmid: 21642685
55. Guo J, et al. J. Clin. Oncol. (2011) pmid: 21690468
56. Debiec-Rychter M, et al. Gastroenterology (2005) pmid: 15685537
57. Demetteo RP, et al. Lancet (2009) pmid: 19303137
58. Faivre S, et al. J. Clin. Oncol. (2005) pmid: 16135502
59. Hotte SJ, et al. J. Clin. Oncol. (2005) pmid: 15659505
60. Alcedo JC, et al. Head Neck (2004) pmid: 15350030
61. Brandwein JM, et al. Leukemia (2011) pmid: 21403650
62. Reardon DA, et al. Br. J. Cancer (2009) pmid: 19904263
63. Lee SJ, et al. Oncologist (2015) pmid: 26424760
64. Llovet JM, et al. Clin. Cancer Res. (2012) pmid: 22374331
65. Zhang HL, et al. Clin Genitourin Cancer (2013) pmid: 23058498
66. Seino S, et al. Gastroenterology (2014) pmid: 25450081
67. Li XF, et al. Med. Oncol. (2009) pmid: 18846437
68. Minor DR, et al. Clin. Cancer Res. (2012) pmid: 22261812
69. Mahipal A, et al. Melanoma Res. (2012) pmid: 23114504
70. Ross JS, et al. J. Clin. Pathol. (2014) pmid: 24978188
71. Xuan H, et al. Histol. Histopathol. (2014) pmid: 23965952
72. Lu HY, et al. Oncol Lett (2012) pmid: 22807968
73. López-Martin A, et al. Lung Cancer (2007) pmid: 17420067
74. Araki K, et al. Lung Cancer (2003) pmid: 12711118
75. Pelosi G, et al. Virchows Arch. (2004) pmid: 15375659
76. Went PT, et al. J. Clin. Oncol. (2004) pmid: 15542802
77. Rossi G, et al. J. Clin. Oncol. (2005) pmid: 16314638
78. Iyoda A, et al. Exp Ther Med (2011) pmid: 22977617
79. Knösel T, et al. J. Cancer Res. Clin. Oncol. (2012) pmid: 22160160
80. Int. J. Biochem. Cell Biol. (1999) pmid: 10582339
81. Semin. Oncol. (2004) pmid: 15175998
82. Zack TI, et al. Nat. Genet. (2013) pmid: 24071852
83. Beroukhim R, et al. Nature (2010) pmid: 20164920
84. Arefi M, et al. Int. J. Hematol. (2012) pmid: 22806436
85. Baccarani M, et al. Haematologica (2007) pmid: 17666373
86. Cassier PA, et al. Clin. Cancer Res. (2012) pmid: 22718859
87. Chalmers ZR, et al. Blood Cancer J (2015) pmid: 25658984
88. Cools J, et al. N. Engl. J. Med. (2003) pmid: 12660384
89. Curtis CE, et al. Br. J. Haematol. (2007) pmid: 17555450
90. Debiec-Rychter M, et al. Eur. J. Cancer (2004) pmid: 15010069
91. Dileo P, et al. Int. J. Cancer (2011) pmid: 20473908
92. Fanta PT, et al. J. Clin. Oncol. (2015) pmid: 24638008
93. Florian S, et al. Leuk. Res. (2006) pmid: 16406018
94. Frenard C, et al. JAAD Case Rep (2016) pmid: 27051816
95. Griffin JH, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12808148
96. Heinrich MC, et al. J. Clin. Oncol. (2003) pmid: 14645423
97. Helbig G, et al. Br. J. Haematol. (2009) pmid: 19120352
98. Helbig G, et al. Am. J. Hematol. (2014) pmid: 24009127
99. Hus M, et al. Leuk. Res. (2011) pmid: 21093052
100. Ikezoe T, et al. Leuk. Res. (2010) pmid: 20303172
101. Intermesoli T, et al. Br. J. Haematol. (2009) pmid: 19735261
102. Jain N, et al. Leuk. Res. (2009) pmid: 19013640
103. Jovanovic JV, et al. Blood (2007) pmid: 17299092
104. Kang HJ, et al. Acta Oncol (2012) pmid: 22150077
105. Klion AD, et al. Blood (2004) pmid: 14504092
106. Kobayashi M, et al. Respirology (2009) pmid: 19192229
107. Kocáková I, et al. Klin Onkol (2014) pmid: 24635438
108. Metzgeroth G, et al. Br. J. Haematol. (2008) pmid: 18950453
109. Murayama Y, et al. World J Gastrointest Oncol (2012) pmid: 22645636
110. Ogbogu PU, et al. J. Allergy Clin. Immunol. (2009) pmid: 19910029
111. Ohnishi H, et al. Br. J. Haematol. (2006) pmid: 16856885
112. Pardanani A, et al. Blood (2003) pmid: 12842979
113. Pardanani A, et al. Blood (2004) pmid: 15284118
114. Qu SQ, et al. Oncotarget (2016) pmid: 27120808
115. Score J, et al. Leukemia (2006) pmid: 16498388
116. Shah S, et al. J Hematol Oncol (2014) pmid: 24669761
117. Sugimoto Y, et al. Cancer Genet (2015) pmid: 26319757
118. Volz HC, et al. Int. J. Cardiol. (2011) pmid: 20609486
119. von Bubnoff N, et al. Leukemia (2005) pmid: 15618966
120. Walz C, et al. Genes Chromosomes Cancer (2006) pmid: 16845659
121. Yoo C, et al. Cancer Res Treat (2016) pmid: 26130666
122. Al-Riyami AZ, et al. Leuk. Lymphoma (2013) pmid: 23157309
123. Lierman E, et al. Blood (2006) pmid: 16645167
124. Lierman E, et al. Leukemia (2009) pmid: 19212337
125. Metzgeroth G, et al. Leukemia (2012) pmid: 21818111
126. Roubaud G, et al. Ann. Oncol. (2012) pmid: 22294526
127. von Bubnoff N, et al. Oncogene (2011) pmid: 20972453
128. Hochhaus A, et al. J. Cancer Res. Clin. Oncol. (2013) pmid: 24057647
129. Tabouret E, et al. Leuk. Res. (2011) pmid: 20832858
130. Dewaele B, et al. Clin. Cancer Res. (2008) pmid: 18794084
131. Weisberg E, et al. Gastroenterology (2006) pmid: 17087936
132. Brohl AS, et al. Clin Sarcoma Res (2015) pmid: 26396737
133. Grellety T, et al. Future Sci OA (2015) pmid: 28031906
134. Kollàr A, et al. Clin Sarcoma Res (2014) pmid: 25905001
135. Jaku et al., 2017; ASCO Abstract 2515
136. Chaudhry A, et al. Cancer Res. (1992) pmid: 1310635
137. Gilbert JA, et al. Endocr. Relat. Cancer (2010) pmid: 20385747
138. Welin S, et al. Neuroendocrinology (2006) pmid: 17047316
139. Int J Clin Exp Pathol (2013) pmid: 23412998
140. Andrae J, et al. Genes Dev. (2008) pmid: 18483217
141. Burford A, et al. PLoS ONE (2013) pmid: 23990986
142. Flavahan WA, et al. Nature (2016) pmid: 26700815
143. Roszik J, et al. Sci Rep (2016) pmid: 26787600
144. Verhaak RG, et al. Cancer Cell (2010) pmid: 20129251
145. Koschmann C, et al. Oncotarget (2016) pmid: 27582545
146. Phillips JJ, et al. Brain Pathol. (2013) pmid: 23438035
147. Puget S, et al. PLoS ONE (2012) pmid: 22389665
148. Loriot Y, et al. N. Engl. J. Med. (2019) pmid: 31340094
149. Tabernero J, et al. J. Clin. Oncol. (2015) pmid: 26324363
150. Karkera JD, et al. Mol. Cancer Ther. (2017) pmid: 28416604
151. Necchi et al., 2018; ESMO Abstract 900P
152. Pal SK, et al. Cancer Discov (2018) pmid: 29848605
153. Pal SK, et al. Cancer (2020) pmid: 32208524
154. Schuler M, et al. Lancet Oncol. (2019) pmid: 31405822
155. Nakanishi Y, et al. Mol. Cancer Ther. (2015) pmid: 25589496
156. Voss MH, et al. Clin. Cancer Res. (2019) pmid: 30745300
157. Papadopoulos KP, et al. Br. J. Cancer (2017) pmid: 28972963
158. Bellmunt J, et al. Br. J. Cancer (2018) pmid: 30220708
159. Palma N, et al. Eur. Urol. (2015) pmid: 25766722



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160. Gozgit JM, et al. Mol. Cancer Ther. (2012) pmid: 22238366
161. Liao RG, et al. Cancer Res. (2013) pmid: 23786770
162. Bellmunt et al., 2018; ASCO Abstract 4534
163. Necchi et al., 2019; ASCO GU Abstract 409
164. Siefker-Radtke et al., 2019; ASCO Abstract 4511
165. Voss et al., 2017; ASCO Abstract 2500
166. Di Stefano AL, et al. Clin. Cancer Res. (2015) pmid: 25609060
167. Farouk Sait S, et al. JCO Precis Oncol (2021) pmid: 34250399
168. Nogova L, et al. J. Clin. Oncol. (2017) pmid: 27870574
169. Slosberg ED, et al. Oncotarget (2018) pmid: 29765547
170. Powers CJ, et al. Endocr. Relat. Cancer (2000) pmid: 11021964
171. Eswarakumar VP, et al. Cytokine Growth Factor Rev. (2005) pmid: 15863030
172. Wesche J, et al. Biochem. J. (2011) pmid: 21711248
173. Binkley MS, et al. Cancer Discov (2020) pmid: 33071215
174. Chowdhry S, et al. Oncogene (2013) pmid: 22964642
175. Abazeed ME, et al. Cancer Res. (2013) pmid: 23980093
176. Chen X, et al. Ann Transl Med (2020) pmid: 32175433
177. Xu X, et al. Oncologist (2020) pmid: 32272498
178. Arbour et al., 2018; IASLC WCLC Abstract MA19.09
179. Zhang C, et al. J Thorac Oncol (2020) pmid: 32471565
180. Shang et al., 2020; WCLC Abstract P75.02
181. Marinelli D, et al. Ann Oncol (2020) pmid: 32866624
182. Cho et al., 2020; AACR Abstract CT084
183. Gwinn DM, et al. Cancer Cell (2018) pmid: 29316436
184. Sayin VI, et al. Elife (2017) pmid: 28967864
185. Romero R, et al. Nat. Med. (2017) pmid: 28967920
186. Skoulidis et al., 2021; ASCO Abstract TPS9627
187. Dai B, et al. Cancer Res. (2013) pmid: 23824739
188. Yoo NJ, et al. Histopathology (2012) pmid: 22348534
189. Lo SC, et al. J. Biol. Chem. (2006) pmid: 17046835
190. Wakabayashi N, et al. Nat. Genet. (2003) pmid: 14517554
191. Kansanen E, et al. Redox Biol (2013) pmid: 24024136
192. Hast BE, et al. Cancer Res. (2013) pmid: 23382044
193. Beuselinck B, et al. Acta Oncol (2018) pmid: 29095068
194. Song Y, et al. Chin. Med. J. (2015) pmid: 26228213
195. Dornbusch J, et al. PLoS ONE (2013) pmid: 24086736
196. Terakawa T, et al. Urol. Oncol. (2013) pmid: 21478036
197. You D, et al. World J Urol (2015) pmid: 24710685
198. Silva E, et al. Breast J () pmid: 25639617
199. Baumgarten P, et al. Neuro-oncology (2016) pmid: 26627848
200. Sathornsumetee S, et al. J. Clin. Oncol. (2008) pmid: 18182667
201. Olafson LR, et al. J Clin Neurosci (2019) pmid: 31582283
202. Duda DG, et al. Oncologist (2010) pmid: 20484123
203. Stremitzer S, et al. Mol. Cancer Ther. (2016) pmid: 27535973
204. Weickhardt AJ, et al. Br. J. Cancer (2015) pmid: 26125443
205. Kopetz S, et al. J. Clin. Oncol. (2010) pmid: 20008624
206. Miles DW, et al. Br. J. Cancer (2013) pmid: 23422754
207. Fountzilas G, et al. Anticancer Res. (2011) pmid: 21868552
208. Gianni L, et al. J. Clin. Oncol. (2013) pmid: 23569311
209. Sánchez-Rovira P, et al. Clin Transl Oncol (2013) pmid: 23397155
210. Cameron D, et al. Lancet Oncol. (2013) pmid: 23932548
211. Mok T, et al. J Thorac Oncol (2014) pmid: 24807156
212. An SJ, et al. Cancer Gene Ther. (2014) pmid: 24577128
213. Bais C, et al. J. Natl. Cancer Inst. (2017) pmid: 29059426
214. Cohen EE, et al. Lancet Oncol. (2009) pmid: 19201650
215. Van Cutsem E, et al. J. Clin. Oncol. (2012) pmid: 22565005
216. Lee EQ, et al. Clin. Cancer Res. (2018) pmid: 29941486
217. Xu L, et al. Cancer Res. (2009) pmid: 19826039
218. Heist RS, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25605928
219. Mairinger FD, et al. J Cancer (2014) pmid: 24959299
220. von Marschall Z, et al. J. Natl. Cancer Inst. (2003) pmid: 12644537
221. Gilbert JA, et al. Pancreas (2013) pmid: 23211371
222. Sartelet H, et al. Hum. Pathol. (2004) pmid: 15492987
223. Fakhari M, et al. J. Pediatr. Surg. (2002) pmid: 11912515
224. Langer I, et al. Med. Pediatr. Oncol. (2000) pmid: 10842244
225. Biol. Pharm. Bull. (2011) pmid: 22130231
226. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
227. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
228. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
229. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
230. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
231. Xu L, et al. Mol. Med. (2001) pmid: 11713371
232. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
233. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
234. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
235. Hajdenberg et al., 2012; ASCO Abstract e15010
236. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
237. Moore et al., 2019; ASCO Abstract 5513
238. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
239. Oza et al., 2015; ASCO Abstract 5506
240. Lee J, et al. Cancer Discov (2019) pmid: 31315834
241. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
242. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
243. Kwok M, et al. Blood (2016) pmid: 26563132
244. Boudny M, et al. Haematologica (2019) pmid: 30975914
245. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
246. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
247. Fernandez-Cuesta L, et al. Nat Commun (2014) pmid: 24670920
248. Higaki-Mori H, et al. Hum. Pathol. (2012) pmid: 22795182
249. Rodig SJ, et al. J. Clin. Invest. (2012) pmid: 23114601
250. Takahashi T, et al. Oncogene (1991) pmid: 1656362
251. Chen H, et al. Endocr. Relat. Cancer (2012) pmid: 22389383
252. Wistuba II, et al. Gynecol. Oncol. (1999) pmid: 9889022
253. Tan HL, et al. Clin. Cancer Res. (2014) pmid: 24323898
254. Yachida S, et al. Am. J. Surg. Pathol. (2012) pmid: 22251937
255. Liu SZ, et al. Asian Pac. J. Cancer Prev. (2013) pmid: 23534765
256. Safatle-Ribeiro AV, et al. Eur J Gastroenterol Hepatol (2007) pmid: 17206073
257. Kobayashi Y, et al. Cancer Sci. (2004) pmid: 15072592
258. Przygodzki RM, et al. Am. J. Pathol. (1996) pmid: 8623922
259. Onuki N, et al. Cancer (1999) pmid: 10091733
260. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
261. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
262. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
263. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
264. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
265. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
266. Pavel M, et al. Ann Oncol (2020) pmid: 32272208
267. Baudin E, et al. Ann Oncol (2021) pmid: 33482246
268. Rindi G, et al. Mod Pathol (2018) pmid: 30140036
269. Nagtegaal ID, et al. Histopathology (2020) pmid: 31433515
270. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
271. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
272. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
273. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
274. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
275. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
276. Lalloo F, et al. Lancet (2003) pmid: 12672316
277. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
278. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
279. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
280. Xie M, et al. Nat. Med. (2014) pmid: 25326804
281. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
282. Severson EA, et al. Blood (2018) pmid: 29678827
283. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
284. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
285. Chabon JJ, et al. Nature (2020) pmid: 32269342
286. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
287. Debiec-Rychter M, et al. Eur. J. Cancer (2006) pmid: 16624552
288. Kamenz T, et al. World J. Gastroenterol. (2006) pmid: 16570351
289. Wang YY, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15650049
290. Samlowski WE, et al. Am. J. Clin. Oncol. (2010) pmid: 20019577
291. Loader DE, et al. J. Am. Acad. Dermatol. (2013) pmid: 24034390
292. Peuvrel L, et al. Eur J Dermatol () pmid: 21926041
293. Spigel DR, et al. J Thorac Oncol (2007) pmid: 17805064
294. Dy GK, et al. Ann. Oncol. (2005) pmid: 16087693
295. Krug LM, et al. Cancer (2005) pmid: 15812822
296. Yao JC, et al. Clin. Cancer Res. (2007) pmid: 17200360
297. Carvajal RD, et al. Clin. Cancer Res. (2015) pmid: 25695690
298. Hochhaus A, et al. J. Cancer Res. Clin. Oncol. (2015) pmid: 26002753
299. Blay JY, et al. Lancet Oncol. (2015) pmid: 25882987
300. Kajimoto N, et al. Int J Clin Exp Pathol (2015) pmid: 26722383
301. Sako H, et al. PLoS ONE (2014) pmid: 25221952
302. Hughes TP, et al. Blood (2014) pmid: 24335106
303. Takahashi N, et al. Biomark Res (2014) pmid: 24650752
304. Reichardt P, et al. Ann. Oncol. (2012) pmid: 22357255
305. Cauchi C, et al. Cancer Chemother. Pharmacol. (2012) pmid: 22119758
306. Villar VH, et al. PLoS ONE (2012) pmid: 22662203
307. Quintás-Cardama A, et al. Nat Clin Pract Oncol (2008) pmid: 18936790
308. Bisagni G, et al. J Thorac Oncol (2009) pmid: 19461405
309. Handolias D, et al. Br. J. Cancer (2010) pmid: 20372153
310. Dişel U, et al. Lung Cancer (2011) pmid: 20970876
311. Park SH, et al. Invest New Drugs (2012) pmid: 22270258

312. Catania C, et al. Onco Targets Ther (2014) pmid: 24855380
313. Guo T, et al. Clin. Cancer Res. (2007) pmid: 17699867
314. Hu S, et al. Mol. Cancer Ther. (2008) pmid: 18483300
315. Chan JA, et al. Cancer Chemother. Pharmacol. (2013) pmid: 23475104
316. Castellano D, et al. Eur. J. Cancer (2013) pmid: 24012098
317. Jeong HK, et al. J. Korean Med. Sci. (2011) pmid: 21738352
318. Lin Y, et al. Onco Targets Ther (2013) pmid: 24235841
319. Quintela-Fandino M, et al. Br. J. Cancer (2013) pmid: 23412107
320. Heinrich MC, et al. J. Clin. Oncol. (2008) pmid: 18955458
321. Buchbinder EI, et al. Cancer (2015) pmid: 26264378
322. Reichardt P, et al. BMC Cancer (2016) pmid: 26772734
323. Hirai F, et al. Mol Clin Oncol (2016) pmid: 27073655
324. Goemans BF, et al. Leuk. Res. (2010) pmid: 20435347
325. Raymond E, et al. N. Engl. J. Med. (2011) pmid: 21306237
326. Faivre S, et al. Ann. Oncol. (2017) pmid: 27836885
327. Kulke MH, et al. J Clin Oncol (2008) pmid: 18612155