



[Oncofocus] Patient Test Report

Primary site	Colon	Tumour %	80
Tumour subtype	Metastatic Colonic Adenocarcinoma	(macrodissected)	
Tissue type	Liver		

Comment:

The DNA and RNA extracted from this sample were of optimal quality. The Oncofocus assay on which the sample was run met all assay specific quality metrics.

221 genes were targeted using 2530 unique amplicons covering oncogenes, fusion genes, genes susceptible to copy number variation and tumour suppressors. Actionable genetic variants detected by Oncofocus are linked to 485 anti-cancer targeted therapies.

The following actionable variants were detected:

Variant Summary

Sample Cancer Type: Colorectal Cancer

In this cancer type
 In other cancer type
 In this cancer type and other cancer types
 Contraindicated
 Both for use and contraindicated
 No evidence

Gene Variant	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials
KRAS p.(G12A) c.35G>C	<input checked="" type="radio"/> (3)	<input checked="" type="radio"/> (2)	<input checked="" type="radio"/> (4)	<input checked="" type="radio"/> (3)	<input checked="" type="radio"/> (32)
RB1 p.(W516Ter) c.1548G>A	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (1)
TP53 p.(R248W) c.742C>T	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (5)
FLT3 amplification	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (2)

EMA: European Medicine Agency, **US-FDA:** United States-Food and Drug Administration, **ESMO:** European Society for Medical Oncology, **US-NCCN:** United States-National Comprehensive Cancer Network. Numbers in parentheses indicate the number of relevant therapies with evidence. Hotspot variants with >10% alternate allele reads, and in >10 unique reads are classified as 'detected' with an assay sensitivity and positive predictive value of 97%. Copy number variants; amplifications of a >5% confidence value of ≥4 after normalization and deletions of ≤1 are classified as present when the tumour% >50%. Gene Fusions are reported when occurring in >20 counts and meeting the thresholds of assay specific internal RNA quality control. With a sensitivity of 99% and PPV of 99%. Supplementary technical information is available upon request.

www.oncologica.com

Other mutations, copy number variations, or fusions that were detected but not classified by the Oncofocus Test as actionable by a known therapeutic targeted agent are not listed in the results section of this report.

Relevant Therapy Summary

● In this cancer type
 ○ In other cancer type
 ● In this cancer type and other cancer types
 ⊘ Contraindicated
 ⚠ Both for use and contraindicated
 ✕ No evidence

KRAS p.(G12A) c.35G>C

Relevant Therapy	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials*
cetuximab	⊘	⊘	⊘	⊘	✕
cetuximab + oxaliplatin	⊘	✕	✕	✕	✕
panitumumab + oxaliplatin	⊘	✕	✕	✕	✕
panitumumab	✕	⊘	⊘	⊘	✕
cetuximab + chemotherapy	✕	✕	⊘	✕	● (II)
panitumumab + chemotherapy	✕	✕	⊘	✕	✕
tyrosine kinase inhibitors	✕	✕	✕	⊘	✕
bevacizumab + chemotherapy	✕	✕	✕	✕	● (III)
AKT inhibitor + MEK inhibitor	✕	✕	✕	✕	● (II/III)
aflibercept + chemotherapy	✕	✕	✕	✕	● (II)
MK-1775 + olaparib	✕	✕	✕	✕	● (II)
palbociclib	✕	✕	✕	✕	● (II)
regorafenib, vorinostat + hydroxychloroquine	✕	✕	✕	✕	● (II)
sorafenib	✕	✕	✕	✕	● (II)
sorafenib + chemotherapy	✕	✕	✕	✕	● (II)
afatinib + selumetinib	✕	✕	✕	✕	● (I/II)
BAL-3833	✕	✕	✕	✕	● (I/II)
dacomitinib + PD-0325901	✕	✕	✕	✕	● (I/II)
lapatinib + trametinib	✕	✕	✕	✕	● (I/II)
LNP3794	✕	✕	✕	✕	● (I/II)
palbociclib + PD-0325901	✕	✕	✕	✕	● (I/II)
ribociclib + trametinib	✕	✕	✕	✕	● (I/II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available. See global clinical trials section in the pages to follow.

www.oncologica.com

Other mutations, copy number variations, or fusions that were detected but not classified by the Oncofocus Test as actionable by a known therapeutic targeted agent are not listed in the results section of this report.

Relevant Therapy Summary (continued)

In this cancer type
 In other cancer type
 In this cancer type and other cancer types
 Contraindicated
 Both for use and contraindicated
 No evidence

KRAS p.(G12A) c.35G>C (continued)

Relevant Therapy	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials*
selumetinib + vistusertib	✗	✗	✗	✗	● (I/II)
atezolizumab + cobimetinib	✗	✗	✗	✗	● (I)
binimetinib + chemotherapy	✗	✗	✗	✗	● (I)
CB-5083	✗	✗	✗	✗	● (I)
crizotinib + PD-0325901	✗	✗	✗	✗	● (I)
HM-95573	✗	✗	✗	✗	● (I)
LXH254	✗	✗	✗	✗	● (I)
MGD007	✗	✗	✗	✗	● (I)
MM-151 + trametinib	✗	✗	✗	✗	● (I)
pembrolizumab + SCH-900353, ridaforolimus + SCH-900353, SCH-900353 + chemotherapy	✗	✗	✗	✗	● (I)
RO-5126766	✗	✗	✗	✗	● (I)
selinexor	✗	✗	✗	✗	● (I)
selumetinib + ciclosporin	✗	✗	✗	✗	● (I)
sEphB4-HSA	✗	✗	✗	✗	● (I)
trametinib + chemotherapy + radiation therapy + surgical intervention	✗	✗	✗	✗	● (I)
trametinib + radiation therapy, trametinib + surgical intervention	✗	✗	✗	✗	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available. See global clinical trials section in the pages to follow.

Relevant Therapy Summary (continued)

In this cancer type
 In other cancer type

I
 In this cancer type and other cancer types

X
 Contraindicated

!
 Both for use and contraindicated

X
 No evidence

RB1 p.(W516Ter) c.1548G>A

Relevant Therapy	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials*
palbociclib	X	X	X	X	● (II)

TP53 p.(R248W) c.742C>T

Relevant Therapy	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials*
MK-1775 + olaparib	X	X	X	X	● (II)
ixazomib + vorinostat	X	X	X	X	● (I)
MK-1775	X	X	X	X	● (I)
pembrolizumab + p53MVA	X	X	X	X	● (I)
SGT-53, SGT-53 + chemotherapy	X	X	X	X	● (I)

FLT3 amplification

Relevant Therapy	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials*
ponatinib	X	X	X	X	● (II)
sorafenib	X	X	X	X	● (II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available. See global clinical trials section in the pages to follow.

Current EMA Information

In this cancer type In other cancer type In this cancer type and other cancer types Contraindicated

EMA information is current as of 2016-10-03. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12A) c.35G>C

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer

Label as of: 2015-02-03

Variant class: KRAS exon 2 mutation

Reference:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000558/WC500029119.pdf

panitumumab + oxaliplatin

Cancer type: Colorectal Cancer

Label as of: 2016-04-15

Variant class: KRAS exon 2 mutation

Reference:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000741/WC500047710.pdf

Current US-FDA Information

In this cancer type In other cancer type In this cancer type and other cancer types Contraindicated

US-FDA information is current as of 2016-10-03. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12A) c.35G>C

cetuximab

Cancer type: Colorectal Cancer

Label as of: 2015-04-10

Variant class: KRAS G12 mutation

Indications and usage:

Erbixux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitation of Use: Erbixux® is not indicated for treatment of *Ras*-mutant colorectal cancer.

Reference:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125084s262lbl.pdf

KRAS p.(G12A) c.35G>C (continued)**⊘ panitumumab**

Cancer type: Colorectal Cancer

Label as of: 2015-03-11

Variant class: KRAS G12 mutation

Indications and usage:

Vectibix® is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of wild-type KRAS (exon 2) metastatic colorectal cancer (mCRC) as determined by an FDA-approved test for this use:

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.

Limitation of Use: Vectibix® is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

Reference:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125147s200lbl.pdf

Current ESMO Information

In this cancer type In other cancer type In this cancer type and other cancer types Contraindicated

ESMO information is current as of 2016-09-07. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12A) c.35G>C

cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

ESMO Recommendation category: II, A

Population segment (Line of therapy):

- Metastatic colorectal cancer (All treatment lines)

Reference: ESMO Clinical Practice Guidelines - Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9.]

cetuximab + chemotherapy

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

ESMO Recommendation category: II, A

Population segment (Line of therapy):

- Metastatic colorectal cancer (All treatment lines)

Reference: ESMO Clinical Practice Guidelines - Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9.]

panitumumab

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

ESMO Recommendation category: II, A

Population segment (Line of therapy):

- Metastatic colorectal cancer (All treatment lines)

Reference: ESMO Clinical Practice Guidelines - Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9.]

KRAS p.(G12A) c.35G>C (continued)**⊘ panitumumab + chemotherapy**

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

ESMO Recommendation category: II, A

Population segment (Line of therapy):

- Metastatic colorectal cancer (All treatment lines)

Reference: ESMO Clinical Practice Guidelines - Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9.]

⊘ cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

ESMO Recommendation category: II, A

Population segment (Line of therapy):

- Metastatic disease (Not specified)

Reference: ESMO Clinical Practice Guidelines - Rectal Cancer [Ann Oncol 2013; 24 (Suppl 6): vi81-vi88.]

⊘ panitumumab

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

ESMO Recommendation category: II, A

Population segment (Line of therapy):

- Metastatic disease (Not specified)

Reference: ESMO Clinical Practice Guidelines - Rectal Cancer [Ann Oncol 2013; 24 (Suppl 6): vi81-vi88.]

Current US-NCCN Information

In this cancer type In other cancer type In this cancer type and other cancer types Contraindicated

US-NCCN information is current as of 2016-09-07. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

KRAS p.(G12A) c.35G>C

cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

US-NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Metastatic colorectal cancer (Not specified)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 2.2016]

cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

US-NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Metastatic colorectal cancer (Not specified)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2016]

panitumumab

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

US-NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Metastatic colorectal cancer (Not specified)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 2.2016]

KRAS p.(G12A) c.35G>C (continued)**⊘ panitumumab**

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

US-NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Metastatic colorectal cancer (Not specified)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2016]

⊘ tyrosine kinase inhibitors

Cancer type: Non-Small Cell Lung Cancer

Variant class: KRAS mutation

Summary:

NCCN Guidelines® do not contain a recommendation regarding KRAS mutations and tyrosine kinase inhibitor (TKI) therapy in non-small cell lung cancer, but include the following evidentiary statements:

- "KRAS mutations are associated with intrinsic EGFR TKI resistance, and KRAS gene sequencing could be useful for the selection of patients as candidates for EGFR TKI therapy. KRAS testing may identify patients who may not benefit from further molecular diagnostic testing."
- "KRAS mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy."
- "TKI therapy is not effective in patients with KRAS mutations and ALK gene rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2016]

Current Global Clinical Trials Information

Global Clinical Trials information is current as of 2016-09-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers'.

KRAS p.(G12A) c.35G>C

NCT02162563

Treatment Strategies in Colorectal Cancer Patients With Initially Unresectable Liver-only Metastases CAIRO5 a Randomized Phase III Study of the Dutch Colorectal Cancer Group (DCCG)

Cancer type: Colorectal Cancer

Variant class: RAS mutation

Other identifiers: CAIRO 5, CAIRO5, DCCG 14-01, EudraCT Number: 2013-005435-24, NL47650.018.14, TrialTroveID-210801

Population segments: Liver mets, Neoadjuvant, Stage IV

Phase: III

Therapy: bevacizumab + chemotherapy

Country: Netherlands

No NCT ID - see other identifier(s)

Molecular selection of therapy in metastatic colorectal cancer: a molecularly stratified randomised controlled trial programme

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: CR13, CRUK/11/054, EudraCT Number: 2012-005111-12, FOCUS-4, FOCUS4, ISRCTN90061546, MREC N° 13/SC/0111, TrialTroveID-187137, UKCRN ID: 14893

Population segments: First line, Stage III, Stage IV

Phase: II/III

Therapy: AKT inhibitor + MEK inhibitor

Country: United Kingdom

NCT02173990

Predictive Value of DCE-US in Patients With Metastatic Colorectal Cancer Treated With First-line Aflibercept-based Treatment. An Exploratory, International, Multicenter, Phase II Study

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: EudraCT number: 2013-004540-33, PULSAR, PULSAR-1303, RECF2410, TrialTroveID-211746

Population segments: First line, Stage IV

Phase: II

Therapy: aflibercept + chemotherapy

Country: France

KRAS p.(G12A) c.35G>C (continued)

No NCT ID - see other identifier(s)

Phase II study of first-line treatment by FOLFOXIRI+bevacizumab in patients with RAS mutant-type metastatic colorectal cancer

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: JACCRO CC-11, TrialTroveID-218272, UMIN000015152

Population segments: First line, Stage IV

Phase: II

Therapy: bevacizumab + chemotherapy

Country: Japan

No NCT ID - see other identifier(s)

A Phase II trial of irinotecan/ S-1 (IRIS) + alfa (panitumumab/ bevacizumab) as second line chemotherapy for metastatic colorectal cancer (mCRC).

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: IRIS-PB trial -Part B-, IRIS-PB trial -Part P-, TrialTroveID-203951, UMIN000009317, UMIN000009318

Population segments: Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: II

Therapy: bevacizumab + chemotherapy

Country: Japan

No NCT ID - see other identifier(s)

A phase II randomized study evaluating the activity and tolerability of first line treatment with bevacizumab + XELOX 2 than FOLFOX 4 + bevacizumab in patients with advanced colorectal cancer with known K-ras mutated tumor

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: 2802, EudraCT Number: 2010-022091-31, GOIM 2802, TrialTroveID-115430

Population segments: First line, Stage III, Stage IV

Phase: II

Therapy: bevacizumab + chemotherapy

Country: Italy

No NCT ID - see other identifier(s)

Phase II study of combination chemotherapy with TS-1/irinotecan and bevacizumab as second-line therapy in patient with K-RAS mutation-type metastatic colorectal cancer

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: SRIM study, TrialTroveID-156536, UMIN000005900

Population segments: Second line or greater/Refractory/Relapsed, Stage IV

Phase: II

Therapy: bevacizumab + chemotherapy

Country: Japan

KRAS p.(G12A) c.35G>C (continued)**No NCT ID - see other identifier(s)**

Non-resectable colorectal liver metastases of KRAS mutant type treated with oxaliplatin, fluorouracil and L-leucovorin plus bevacizumab induction toward liver R0 resection trial

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: NEXTO-mt, TrialTroveID-179078, UMIN000009530

Population segments: Adjuvant, Liver mets, Neoadjuvant, Stage IV

Phase: II

Therapy: bevacizumab + chemotherapy

Country: Japan

NCT01802645

Open, Randomized, Multicenter Phase II Trial With Cetuximab /5-FU/FA/ Irinotecan or Cetuximab/5-FU/FA / Irinotecan/Oxaliplatin in K-ras/B-raf Wild Type Patients or With Irinotecan/Oxaliplatin/5-FU/FA With or Without Bevacizumab in K-ras Mutant Patients as Neoadjuvant Treatment in Patients With Non- Resectable Colorectal Liver Metastases.

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: CELIM 2- study, CELIM2, DRKS00010758, EudraCT Number: 2011-003288-31, TrialTroveID-141012, TUD-CELIM2-050

Population segments: Adjuvant, Liver mets, Neoadjuvant, Stage IV

Phase: II

Therapy: bevacizumab + chemotherapy

Country: Germany

NCT01858649

Randomized Phase II Study Comparing Pathological Responses Observed on Colorectal Cancer Metastases Resected After Preoperative Treatment Combining Bevacizumab With FOLFOX or FOLFIRI

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: BEV-ONCO2012, CTBE2013000207, EudraCT Number: 2012-005376-34, TrialTroveID-186955

Population segments: Neoadjuvant, Stage IV

Phase: II

Therapy: bevacizumab + chemotherapy

Country: Belgium

KRAS p.(G12A) c.35G>C (continued)**NCT01037790**

Phase II Trial of the Cyclin-Dependent Kinase Inhibitor PD 0332991 in Patients With Cancer

Cancer type: Colorectal Cancer**Variant class:** KRAS mutation**Other identifiers:** NCI-2009-01467, Study 1006, TrialTroveID-120590, UPCC 03909, UPCC03909**Population segments:** HER2 negative, HER2 positive, Metastatic, Second line or greater/Refractory/Relapsed, Stage III, Stage IV, Triple receptor negative**Phase:** II**Therapy:** palbociclib**Country:** United States**US State:** PA**US Contact:** Peter O'Dwyer [855-216-0098; PennCancerTrials@emergingmed.com]**NCT02316340**

Modulation of Autophagy: A Clinical Study of Vorinostat Plus Hydroxychloroquine Versus Regorafenib in Refractory Metastatic Colorectal Cancer (mCRC) Patients

Cancer type: Colorectal Cancer**Variant class:** KRAS mutation**Other identifiers:** CTMS 14-2015, CTMS# 14-2015, HSC20150178H, NCI-2015-00175, NCI-2015-00203, TrialTroveID-243207**Population segments:** Second line or greater/Refractory/Relapsed, Stage IV**Phase:** II**Therapies:** regorafenib, vorinostat + hydroxychloroquine**Country:** United States**US State:** TX**US Contact:** Epp Goodwin [210-450-5798; CTRCCReferral@uthscsa.edu]**NCT01675999**

PRODIGE 22-ECKINOXE: Randomized Phase II Trial of Neoadjuvant FOLFOX 4 Versus FOLFOX 4 With Cetuximab Versus Immediate Surgery in Locally Advanced Colon Cancer ECKINOXE : EXperimental Colon KIRAS-status based Neoadjuvant OXwith or without treatment aliplatin Erbitux

Cancer type: Colorectal Cancer**Variant class:** RAS mutation**Other identifiers:** ECKINOXE, ECKINOXE # PRODIGE 22, ECKINOXE PRODIGE 22 FFCD 1003, EudraCT Number: 2011-001519-29, P100131, PHRC10_02-42, PRODIGE 22-ECKINOXE, PRODIGY 22 - FFCD 1003, RECF2082, TrialTroveID-173718**Population segments:** Adjuvant, Neoadjuvant, Stage II, Stage III**Phase:** II**Therapy:** cetuximab + chemotherapy**Country:** France

KRAS p.(G12A) c.35G>C (continued)**NCT02450656**

Phase I/II study with the combination of afatinib and selumetinib in advanced KRAS mutant positive and PIK3CA wildtype colorectal, non-small cell lung and pancreatic cancer

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

Other identifiers: EudraCT Number: 2014-001855-22, M14AFS, NL49983.031.14, TrialTroveID-251759

Population segments: KRAS, Second line or greater/Refractory/Relapsed, Stage II, Stage III, Stage IV

Other inclusion criteria: PIK3CA wild type

Phase: I/II

Therapy: afatinib + selumetinib

Country: Netherlands

NCT02039336

Phase I/II Study With the Combination of Dacomitinib and PD-0325901 in Metastatic KRAS Mutation Positive Colorectal, Non-small Cell Lung and Pancreatic Cancer

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

Other identifiers: EudraCT Number: 2013-003299-10, M13DAP, NL45985.031.13, TrialTroveID-200856

Population segments: KRAS, Line of therapy N/A, Stage III, Stage IV

Phase: I/II

Therapy: dacomitinib + PD-0325901

Country: Netherlands

NCT02230553

Phase I/II study with lapatinib plus trametinib in patients with metastatic KRAS mutant colorectal, non-small cell lung and pancreatic cancer

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

Other identifiers: EudraCT Number: 2014-002209-39, M14LTK, NL49551.031.14, TrialTroveID-214278

Population segments: KRAS, Second line or greater/Refractory/Relapsed, Stage IV

Other inclusion criteria: PIK3CA wild type

Phase: I/II

Therapy: lapatinib + trametinib

Country: Netherlands

KRAS p.(G12A) c.35G>C (continued)**NCT02703571**

A Phase I/II Study of Safety and Efficacy of Ribociclib (LEE011) in Combination With Trametinib (TMT212) in Patients With Metastatic or Advanced Solid Tumors

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: CTMT212X2106, EudraCT Number: 2015-005019-34, TrialTroveID-274520

Population segments: Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I/II

Therapy: ribociclib + trametinib

Countries: Netherlands, United States

US States: AR, FL

US Contact: Novartis Pharmaceuticals [888-669-6682]

NCT02583542

A Phase Ib/Ila Study of AZD2014 in Combination With Selumetinib in Patients With Advanced Cancers.

Cancer type: Colorectal Cancer

Variant class: RAS/RAF/MEK/ERK pathway

Other identifiers: 009896QM, EudraCT Number: 2014-002613-31, IRAS ID 172356, Torcmek, TrialTroveID-265019, UKCRN ID:18725

Population segments: EGFR, FGFR, HER2 negative, HER2 positive, KRAS, Second line or greater/Refractory/Relapsed, Squamous Cell, Stage III, Stage IV, Triple receptor negative

Phase: I/II

Therapy: selumetinib + vistusertib

Country: United Kingdom

NCT01988896

A Phase Ib Study of the Safety and Pharmacology of Atezolizumab Administered With Cobimetinib in Patients With Locally Advanced or Metastatic Solid Tumors

Cancer type: Colorectal Cancer

Variant class: KRAS G12 mutation

Other identifiers: 13-223, 14-301, 20132268, CT672, DFCI: 14-301, EudraCT Number: 2013-003329-27, GP28363, GP28363-V2, HIC: 1403013518, NCI-2014-00166, Octopus, TrialTroveID-197176

Population segments: ALK, EGFR, KRAS, Second line or greater/Refractory/Relapsed, Stage I, Stage II, Stage III, Stage IV

Phase: I

Therapy: atezolizumab + cobimetinib

Countries: Australia, Canada, Germany, Republic of Korea, Singapore, United States

US States: CA, CO, CT, MA, NC, NY, TX, WA

US Contact: Clinical Trials Hoffmann-La Roche [888-662-6728; global.roche.genentechtrials@roche.com]

KRAS p.(G12A) c.35G>C (continued)**NCT02510001**

A Phase I Study of MEK 1/2 Inhibitor PD-0325901 With cMET Inhibitor PF-03241066 in RASMT and RASWT (With Aberrant c-MET) Colorectal Cancer Patients

Cancer type: Colorectal Cancer

Variant class: KRAS G12 mutation

Other identifiers: 17363, EudraCT Number: 2014-000463-40, ISRCTN18043777, MErCuRIC, MErCuRIC1, OCTO-049, TrialTroveID-217604, UKCRN ID:17363

Population segments: First line, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: crizotinib + PD-0325901

Country: United Kingdom

NCT01740648

A Phase I Trial of MEK Inhibitor Trametinib in Combination With Neoadjuvant 5-Fluorouracil Chemoradiation in the Treatment of KRAS, BRAF, and NRAS-MUTANT Rectal Cancers

Cancer type: Colorectal Cancer

Variant class: KRAS G12 mutation

Other identifiers: 2012C0086, 201403053, NCCNGSK10033, NCI-2012-02158, OSU-12054, TrialTroveID-174199

Population segments: Line of therapy N/A, Neoadjuvant, Stage II, Stage III

Phase: I

Therapy: trametinib + chemotherapy + radiation therapy + surgical intervention

Country: United States

US State: OH

US Contact: Ohio State University Comprehensive Cancer Center [800-293-5066; Jamesline@osumc.edu]

NCT02243917

A Phase 1, Open-Label, Dose Escalation and Dose Expansion Study Evaluating the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Effects of Orally Administered CB-5083 in Subjects With Advanced Solid Tumors

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

Other identifiers: 149511, CLC-101, TrialTroveID-216163

Population segments: Second line or greater/Refractory/Relapsed, Stage II, Stage III, Stage IV

Phase: I

Therapy: CB-5083

Country: United States

US States: AZ, CA, CO, GA, PA

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

KRAS p.(G12A) c.35G>C (continued)**NCT02538627**

A Phase 1 Study Evaluating the Safety, Pharmacology and Preliminary Activity of the Co-Administration of MM-151 and MM-121 in Heregulin Positive Cancer Patients

Cancer type: Colorectal Cancer

Variant class: KRAS activating mutation

Other identifiers: MM-151-01-01-02, NCI-2015-01527, TrialTroveID-264006, VICCPHI1598

Population segments: Second line or greater/Refractory/Relapsed, Squamous Cell, Stage III, Stage IV

Phase: I

Therapy: MM-151 + trametinib

Country: United States

US States: CO, GA, IL, TN

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT02613650

A Phase Ib Trial of a Combination of FOLFIRI With MEK162 in Patients With Advanced KRAS Positive Metastatic Colorectal Cancers

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: CMEK162AUS12T, HCI87144, MEK162/FOLFIRI, NCI-2016-00331, TrialTroveID-268582

Population segments: Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: binimetinib + chemotherapy

Country: United States

US State: UT

US Contact: Alexis Mollard [801-587-5598; alexis.mollard@hci.utah.edu]

NCT02405065

Phase I Study to Assess the Safety, Tolerability and Pharmacokinetics and Anti-tumor Activity of HM95573 in Solid Tumors

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: HM-RAFI-101, TrialTroveID-220532

Population segments: KRAS, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: HM-95573

Country: Republic of Korea

KRAS p.(G12A) c.35G>C (continued)**NCT02248805**

A Phase I, First-in-Human, Open Label, Dose Escalation Study of MGD007, A Humanized gpA33 x CD3 Dual-Affinity Re-Targeting (DART) Protein in Patients With Relapsed/Refractory Metastatic Colorectal Carcinoma.

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: 00056149, 14-524, AAAP4552, CP-MGD007-01, J14126, NCI-2015-00188, TrialTroveID-208327

Population segments: Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: MGD007

Country: United States

US States: MA, MD, NC, OR

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

No NCT ID - see other identifier(s)

A Phase I Study to Evaluate the Safety, Tolerability and Efficacy of MK-8353 Combination Therapies in Subjects With Advanced Solid Tumors

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: EudraCT Number: 2012-002695-13, MK8353-010, NL41947.031.12, TrialTroveID-222700

Population segments: KRAS, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapies: pembrolizumab + SCH-900353, ridaforolimus + SCH-900353, SCH-900353 + chemotherapy

Country: Netherlands

NCT02078349

An Investigator Sponsored Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses Followed by Dose Expansion of the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) in Asian Patients With Advanced or Metastatic Solid Tumor Malignancies

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: 2013/01034, KPT330-A1, TrialTroveID-203656

Population segments: Aggressive, Diffuse large B-cell lymphoma (DLBCL), KRAS, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: selinexor

Country: Singapore

KRAS p.(G12A) c.35G>C (continued)**NCT01642342**

A First-In-Human Phase I Study of sEphB4-HSA in Patients With Advanced Solid Tumors With Expansion at the Maximum Tolerated Dose (MTD) or Recommended Phase II Dose (RP2D).

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Other identifiers: OC-11-3, NCI-2012-00971, TrialTroveID-171511

Population segments: Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: sEphB4-HSA

Country: United States

US State: CA

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT02188264

A Phase IB Study of the Combination of AZD6244 Hydrogen Sulfate (Selumetinib) and Cyclosporin A (CsA) in Patients With Advanced Solid Tumors With an Expansion Cohort in Metastatic Colorectal Cancer

Cancer type: Colorectal Cancer

Variant class: RAS mutation

Other identifiers: 051406, 13-2628, 201409113, 9571, NCI-2014-01484, NCI-9571-CIRB, NCI/CTEP #9571, NCI9571, P9571_A01PAMDREVV01, TrialTroveID-212843

Population segments: Stage IV, Second line or greater/Refractory/Relapsed, Stage III

Exclusion criteria variant class: BRAF mutation

Phase: I

Therapy: selumetinib + ciclosporin

Country: United States

US States: CO, MO, NC, NJ, OH, PA, TX

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT02576444

A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant classes: KRAS & TP53 mutation

Other identifiers: 1508016363, OLAPCO, TrialTroveID-266161

Population segments: First line, Second line or greater/Refractory/Relapsed, Stage IV

Phase: II

Therapy: MK-1775 + olaparib

Country: United States

US State: CT

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

KRAS p.(G12A) c.35G>C (continued)**NCT02029001**

A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors MOST: My own specific treatment

Cancer type: Unspecified Solid Tumor

Variant class: KRAS mutation

Other identifiers: ET12-081, EudraCT number: 2012-004510-34, MOST, ProfiLER, TrialTroveID-200294

Population segments: Maintenance/Consolidation, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Exclusion criteria variant class: BRAF V600 mutation

Phase: II

Therapy: sorafenib

Country: France

NCT02747537

Phase II Clinical Trial Treating Relapsed/Recurrent/Refractory Pediatric Solid Tumors With the Genomically-Targeted Agent Sorafenib in Combination With Irinotecan

Cancer type: Unspecified Solid Tumor

Variant class: RAS mutation

Other identifiers: 201605006, NCI-2016-00680, TrialTroveID-277232

Population segments: (N/A), Second line or greater/Refractory/Relapsed

Phase: II

Therapy: sorafenib + chemotherapy

Country: United States

US State: MO

US Contact: Dr. Robert Hayashi [314-454-6018; hayashi_r@kids.wustl.edu]

NCT02022982

Phase I/II Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the MEK Inhibitor PD-0325901 for Patients with KRAS Mutant Non-Small Cell Lung Cancer and Other Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: KRAS mutation

Other identifiers: 13-506, NCI-2014-00940, TrialTroveID-200043

Population segments: KRAS, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I/II

Therapy: palbociclib + PD-0325901

Country: United States

US State: MA

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

KRAS p.(G12A) c.35G>C (continued)**NCT02437227**

A Phase 1, First in Man, Dual Centre, Open-label Dose Escalation Study With Expansion to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of CCT3833 (BAL3833), a panRAF Inhibitor, Given Orally in Patients With Advanced Solid Tumours, Including Metastatic Melanoma

Cancer type: Unspecified Solid Tumor

Variant class: RAS mutation

Other identifiers: 4232, PanRAF, TrialTroveID-257046

Population segments: Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I/II

Therapy: BAL-3833

Country: United Kingdom

No NCT ID - see other identifier(s)

A Phase I/II Study of LNP3794 in Patients with Advanced Solid Tumors having RAS/ BRAF Mutations

Cancer type: Unspecified Solid Tumor

Variant class: RAS mutation

Other identifier: TrialTroveID-250171

Population segments: Line of therapy N/A, Stage III, Stage IV

Phase: I/II

Therapy: LNP3794

Country: United Kingdom

NCT02407509

A Phase I Trial of RO5126766 (a Dual RAF/MEK Inhibitor) Exploring Intermittent, Oral Dosing Regimens in Patients With Solid Tumours or Multiple Myeloma

Cancer type: Unspecified Solid Tumor

Variant class: KRAS mutation

Other identifiers: CCR3808, DDU RAF/MEK, EudraCT Number: 2012-001040-22, TrialTroveID-206542

Population segments: Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: RO-5126766

Country: United Kingdom

KRAS p.(G12A) c.35G>C (continued)**NCT02015117**

A Phase 1 Study of Trametinib in Combination With Radiation Therapy for Brain Metastases

Cancer type: Unspecified Cancer

Variant class: KRAS mutation

Other identifiers: 2013C0115, 9458, NCI-2013-02343, OSU 13197, OSU-13197, TrialTroveID-199440

Population segments: CNS mets, First line, Line of therapy N/A, Stage IV

Phase: I

Therapies: trametinib + radiation therapy, trametinib + surgical intervention

Country: United States

US States: IL, OH

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT02607813

A Phase I Dose Finding Study of Oral LXH254 in Adult Patients With Advanced Solid Tumors Harboring MAPK Pathway Alterations

Cancer type: Unspecified Solid Tumor

Variant class: RAS/RAF/MEK/ERK pathway

Other identifiers: 2015-0913, CLXH254X2101, EudraCT Number: 2015-003421-33, NCI-2015-02280, REec-2016-2132, TrialTroveID-268216

Population segments: Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: LXH254

Countries: Canada, Germany, Japan, Netherlands, Spain, United States

US States: NY, TX

US Contact: Novartis Pharmaceuticals [888-669-6682]

RB1 p.(W516Ter) c.1548G>A**NCT01037790**

Phase II Trial of the Cyclin-Dependent Kinase Inhibitor PD 0332991 in Patients With Cancer

Cancer type: Unspecified Solid Tumor**Variant class:** G1/S cell cycle pathway**Other identifiers:** NCI-2009-01467, Study 1006, TrialTroveID-120590, UPCC 03909, UPCC03909**Population segments:** HER2 negative, HER2 positive, Metastatic, Second line or greater/Refractory/Relapsed, Stage III, Stage IV, Triple receptor negative**Phase:** II**Therapy:** palbociclib**Country:** United States**US State:** PA**US Contact:** Peter O'Dwyer [855-216-0098; PennCancerTrials@emergingmed.com]**TP53 p.(R248W) c.742C>T****NCT02432963**

A Phase I Study of a p53MVA Vaccine in Combination With Pembrolizumab

Cancer type: Colorectal Cancer**Variant class:** TP53 mutation**Other identifiers:** 116634, 122284, 122771, 124524, 15002, NCI-2015-00653, TrialTroveID-256830**Population segments:** HER2 negative, Second line or greater/Refractory/Relapsed, Stage III, Stage IV, Triple receptor negative, Unresectable**Phase:** I**Therapy:** pembrolizumab + p53MVA**Country:** United States**US State:** CA**US Contact:** Vincent Chung [800-826-4673]

TP53 p.(R248W) c.742C>T (continued)**NCT02576444**

A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant classes: KRAS & TP53 mutation

Other identifiers: 1508016363, OLAPCO, TrialTroveID-266161

Population segments: First line, Second line or greater/Refractory/Relapsed, Stage IV

Phase: II

Therapy: MK-1775 + olaparib

Country: United States

US State: CT

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT02042989

A Phase I Study of MLN9708 and Vorinostat to Target Autophagy in Patients With Advanced p53 Mutant Malignancies

Cancer type: Unspecified Solid Tumor

Variant class: TP53 mutation

Other identifiers: 2013-0511, NCI-2014-01091, TrialTroveID-201319

Population segments: Line of therapy N/A, Stage III, Stage IV

Phase: I

Therapy: ixazomib + vorinostat

Country: United States

US State: TX

US Contact: Dr. Siqing Fu [713-563-1930]

NCT02610075

A Phase Ib Study to Determine the Maximum Tolerated Dose (MTD) of AZD1775 Monotherapy in Patients With Locally Advanced or Metastatic Solid Tumours.

Cancer type: Unspecified Solid Tumor

Variant class: TP53 mutation

Other identifiers: D6015C00003, REFMAL 398, TrialTroveID- 268385

Population segments: Liver mets, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: MK-1775

Country: United States

US States: CO, TN

US Contact: AstraZeneca Clinical Study Information Center [877-240-9479; information.center@astrazeneca.com]

TP53 p.(R248W) c.742C>T (continued)**NCT02354547**

A Phase I Study of SGT-53, a TfRscFv-Liposome-p53 Complex, in Children with Refractory or Recurrent Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: TP53 mutation

Other identifiers: 1405-1316, SGT53-01-2, TrialTroveID-251586

Population segments: (N/A), Second line or greater/Refractory/Relapsed

Phase: I

Therapies: SGT-53, SGT-53 + chemotherapy

Country: United States

US State: TX

US Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

FLT3 amplification**NCT02029001**

A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors MOST: My own specific treatment

Cancer type: Unspecified Solid Tumor

Variant class: FLT3 amplification

Other identifiers: ET12-081, EudraCT number: 2012-004510-34, MOST, ProfILER, TrialTroveID-200294

Population segments: Maintenance/Consolidation, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Exclusion criteria variant class: BRAF V600 mutation

Phase: II

Therapy: sorafenib

Country: France

NCT02272998

Phase II Study Of Ponatinib For Advanced Cancers With Genomic Alterations In Fibroblastic Growth Factor Receptor (FGFR) And Other Genomic Targets (KIT, Pdgfra, RET FLT3, ABL1)

Cancer type: Unspecified Solid Tumor

Variant class: FLT3 aberration

Other identifiers: 14078, 2014C0143, NCI-2014-01499, OSU-14078, TrialTroveID-219466

Population segments: Advanced, Second line or greater/Refractory/Relapsed, Stage IV

Phase: II

Therapy: ponatinib

Country: United States

US States: MI, OH

US Contact: The Ohio State University Comprehensive Cancer Center [800-293-5066]

Appendix: Evidence Summary by Variant Class

A variant class hierarchy was created to summarize gene variants with associated clinical evidence. Evidence items refers to citations across the different global data sources.

KRAS p.(G12A) c.35G>C

Variant Class	Evidence Items
RAS/RAF/MEK/ERK pathway	2
↳ RAS mutation	6
↳ RAS activating mutation	0
↳ KRAS activating mutation	1
↳ KRAS G12 mutation	5
↳ KRAS mutation	31
↳ KRAS activating mutation	1
↳ KRAS G12 mutation	5
↳ KRAS exon 2 mutation	10
↳ KRAS G12 mutation	5

RB1 p.(W516Ter) c.1548G>A

Variant Class	Evidence Items
G1/S cell cycle pathway	1

TP53 p.(R248W) c.742C>T

Variant Class	Evidence Items
TP53 mutation	6

Appendix: Evidence Summary by Variant Class (continued)

A variant class hierarchy was created to summarize gene variants with associated clinical evidence. Evidence items refers to citations across the different global data sources.

FLT3 amplification

Variant Class	Evidence Items
FLT3 aberration	1
↳ FLT3 amplification	1

Appendix: Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency Transcript	Variant Effect
KRAS	p.(G12A)	c.35G>C	COSM522	chr12:25398284	40.60% NM_033360.3	missense
RB1	p.(W516Ter)	c.1548G>A	.	chr13:48955432	14.00% NM_000321.2	nonsense
TP53	p.(R248W)	c.742C>T	COSM10656	chr17:7577539	48.12% NM_000546.5	missense

Copy Number Variations

Gene	Locus	Copy Number
FLT3	chr13:28579521	6.45

