Medical Laboratory
Accredited to ISO15189:2012

UKAS MEDICAL 9376

oncologica®

Leading a new era of precision oncology

Oncofocus®

Precision Oncology

ONCOFOCUS® TEST REPORT

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Table of Contents

Table of Contents	Page
Biomarker Descriptions	3
Relevant Therapy Summary	4
Relevant Therapy Details	6
Clinical Trials	20
Variant Details	29

Patient demographics

Surname	-	**Requester**	-
Forename	-	**Contact details**	-
DOB	-	**Date requested**	-
Gender	-		
Histology #	-	**Tumour %**	90%
Primary site	Primary Brain Tumour	**Tumour % (macrodissected)**	-
Tumour subtype	Glioblastoma		
Tissue Type	Posterio/inferior Brain Tumour		

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.

Oncofocus currently targets 505 genes covering oncogenes, fusion genes, genes susceptible to copy number variation and tumour suppressors. Actionable genetic variants detected by Oncofocus are currently linked to 764 anti-cancer targeted therapies/therapy combinations.

The clinically significant bio-markers identified in this case are summarised on page 2

Within the 'Current Clinical Trials Information' section of this report, starting on page 20, the NCT numbers are hyperlinks to the clinicaltrials.gov webpages which should be accessed to gain further trial specific information

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Clinically Significant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
BRAF p.(V600E) c.1799T>A	Clinical trials and/or off-label	binimetinib + encorafenib [1, 2] cobimetinib + vemurafenib [1, 2] dabrafenib + trametinib [1, 2] dabrafenib [1, 2] trametinib [1, 2] vemurafenib [1, 2] BRAF inhibitor + MEK inhibitor cetuximab + vemurafenib + chemotherapy panitumumab + vemurafenib + chemotherapy	14
PIK3CB p.(L1049R) c.3146T>G	Clinical trials and/or off-label	Clinical trials and/or off-label	5

Sources included in relevant therapies: EMA1, FDA2, ESMO, NCCN

Hotspot variants with >10% alternate allele reads are classified as 'detected' with an assay sensitivity and positive predictive value(PPV) of 99%. Copy number variants; amplifications of CN> 6 with the 5% confidence value of ≥4 after normalization and deletions with 95% CI ≤1 are classified as present when the tumour% >50% with a sensitivity of 80% and PPV 100%. Gene Fusions are reported when occurring in >40 counts and meeting the thresholds of assay specific internal RNA quality control with a sensitivity of 92% and PPV of 99%.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. Supplementary technical information is available upon request.

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Biomarker Descriptions

BRAF (B-Raf proto-oncogene, serine/threonine kinase)

Background: The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1 (CRAF). BRAF is among the most commonly mutated kinases in cancer[1]. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, differentiation, and survival[2].

Alterations and prevalence: Recurrent somatic mutations in BRAF are observed in 40-60% of melanoma and thyroid cancer, approximately 10% of colorectal cancer, and about 2% of non-small cell lung cancer (NSCLC)[3,4,5,6,7]. The most recurrent somatic BRAF mutation across diverse cancer types is V600E in exon 15, which results in constitutive kinase activity by relieving negative regulatory inhibition[8]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer and prevalent in histiocytic neoplasms[9,10,11]. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11 as well as additional codons flanking V600 in the activation loop[8]. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer[4,7]. Chromosomal translocations generating BRAF fusions with a range of partner genes are uncommon (about 0.5%) but have been described in melanoma that lack V600 mutations, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[12,13,14,15,16]. BRAF fusions retain the kinase domain but lack the autoinhibitory N-terminal domain of BRAF[12,14].

Potential clinical relevance: Vemurafenib[17] (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation. Subsequently, BRAF kinase inhibitors including dabrafenib[18] (2013) and encorafenib[19] (2018) were approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Due to the tight coupling of RAF and MEK, several MEK inhibitors have been approved for patients harboring BRAF alterations. Trametinib[20] (2013) and binimetinib[21] (2018) were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC. The combinations of dabrafenib and trametinib (2015) and vemurafenib and cobimetinib[22] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017) with a BRAF V600E mutation. BRAF amplification, alternative splice transcripts, and BRAF fusions are suggested mechanisms of resistance to BRAF targeted therapy in melanoma[23,24,25,26]. Other mechanisms of resistance include activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2) as well as activation of PI3K signaling[25,27,28,29,30]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[16].

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Tier Criteria Met

Genomic Alteration	Tier Classification for Glioblastoma
BRAF p.(V600E) c.1799T>A Tier: IIC	IIC: Biomarker predicts response or resistance to EMA or FDA approved therapies in other cancer types IIC: Biomarker is included in ESMO or NCCN guidelines that predict response or resistance to therapies in other cancer types IIC: Biomarker is an inclusion criteria for clinical trials
PIK3CB p.(L1049R) c.3146T>G Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials

Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

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

BRAF p.(V600E) c.1799T>A

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
dabrafenib + trametinib	○	○	○	○	✖
cobimetinib + vemurafenib	○	○	✖	○	● (II)
binimetinib + encorafenib	○	○	✖	○	✖
dabrafenib	○	○	✖	○	✖
vemurafenib	○	○	✖	○	✖
trametinib	○	○	✖	✖	✖
BRAF inhibitor + MEK inhibitor	✖	✖	○	✖	✖
cetuximab + vemurafenib + irinotecan	✖	✖	✖	○	✖
panitumumab + vemurafenib + irinotecan	✖	✖	✖	○	✖
cobimetinib + vemurafenib, dabrafenib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
cobimetinib	✖	✖	✖	✖	● (I/II)
abemaciclib + LY3214996 , LY3214996 , LY3214996 + chemotherapy, LY3214996 + midazolam	✖	✖	✖	✖	● (I)
belvarafenib	✖	✖	✖	✖	● (I)
belvarafenib + cobimetinib	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Referring pathology dept: -

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

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

BRAF p.(V600E) c.1799T>A (continued)

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
everolimus + RO-5126766, RO-5126766	✖	✖	✖	✖	● (I)
HL-085 + vemurafenib	✖	✖	✖	✖	● (I)
KO-947	✖	✖	✖	✖	● (I)
LXH254 , LXH254 + spartalizumab	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)

PIK3CB p.(L1049R) c.3146T>G

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
capivasertib + olaparib	✖	✖	✖	✖	● (II)
atezolizumab + ipatasertib	✖	✖	✖	✖	● (I/II)
AZD8186, AZD8186 + abiraterone acetate + steroid, AZD8186 + vistusertib	✖	✖	✖	✖	● (I)
gedatolisib + palbociclib	✖	✖	✖	✖	● (I)
palbociclib + pictilisib, palbociclib + taselisib	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Relevant Therapy Details

Current EMA Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

EMA information is current as of 2019-05-29. For the most up-to-date information, search www.ema.europa.eu/ema.

BRAF p.(V600E) c.1799T>A

binimetinib + encorafenib

Cancer type: Melanoma **Label as of:** 2019-05-10 **Variant class:** BRAF V600E mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information_en.pdf

binimetinib + encorafenib

Cancer type: Melanoma **Label as of:** 2019-02-12 **Variant class:** BRAF V600E mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/mektovi-epar-product-information_en.pdf

cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2018-08-31 **Variant class:** BRAF V600E mutation

Reference:

https://www.ema.europa.eu/documents/product-information/cotellic-epar-product-information_en.pdf

dabrafenib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer **Label as of:** 2018-09-11 **Variant class:** BRAF V600E mutation

Reference:

https://www.ema.europa.eu/documents/product-information/tafinlar-epar-product-information_en.pdf

trametinib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer **Label as of:** 2019-04-08 **Variant class:** BRAF V600E mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/mekinist-epar-product-information_en.pdf

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

vemurafenib

Cancer type: Melanoma **Label as of:** 2018-08-23 **Variant class:** BRAF V600 mutation

Reference:

https://www.ema.europa.eu/documents/product-information/zelboraf-epar-product-information_en.pdf

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

FDA information is current as of 2019-05-29. For the most up-to-date information, search www.fda.gov.

BRAF p.(V600E) c.1799T>A

○ binimetinib + encorafenib

Cancer type: Melanoma **Label as of:** 2019-01-23 **Variant class:** BRAF V600E mutation

Indications and usage:
MEKTOVI® is a kinase inhibitor indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210498lbl.pdf

○ binimetinib + encorafenib

Cancer type: Melanoma **Label as of:** 2019-01-23 **Variant class:** BRAF V600E mutation

Indications and usage:

BRAFTOVI™ is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

Limitations of Use: BRAFTOVI™ is not indicated for treatment of patients with wild-type BRAF melanoma.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210496s001lbl.pdf

○ cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2018-01-26 **Variant class:** BRAF V600E mutation

Indications and usage:

COTELLIC® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206192s002lbl.pdf

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

BRAF p.(V600E) c.1799T>A (continued)

dabrafenib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Thyroid Cancer **Label as of:** 2018-05-04 **Variant class:** BRAF V600E mutation

Indications and usage:

TAFINLAR® is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

TAFINLAR® is indicated, in combination with trametinib, for:

- the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
- the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.

Limitations of Use: TAFINLAR® is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202806s010lbl.pdf

trametinib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Thyroid Cancer **Label as of:** 2018-05-04 **Variant class:** BRAF V600E mutation

Indications and usage:

MEKINIST® is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

MEKINIST® is indicated, in combination with dabrafenib, for:

- the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
- the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options

Limitations of Use: MEKINIST® is not indicated for treatment of patients with melanoma who have progressed on prior BRAF-inhibitor therapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204114Orig1s009lbl.pdf

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

vemurafenib

Cancer type: Melanoma **Label as of:** 2017-11-06 **Variant class:** BRAF V600E mutation

Indications and usage:

- ZELBORAF® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
- ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation.

Limitation of Use: ZELBORAF® is not indicated for treatment of patients with wild-type BRAF melanoma.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202429s016lbl.pdf

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

ESMO information is current as of 2019-02-14. For the most up-to-date information, search www.esmo.org.

BRAF p.(V600E) c.1799T>A

○ BRAF inhibitor + MEK inhibitor

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

ESMO Level of Evidence/Grade of Recommendation: II / B

Population segment (Line of therapy):
- Stage IV Metastatic Melanoma; BRAF-V600 mutant (First and second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Ann Oncol (2015) 26 (suppl 5): v126-v132. (eUpdate: 19 September 2016; 19 September 2016)]

○ dabrafenib + trametinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600 mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- Stage IV Non-Small Cell Lung Cancer; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 score: 2 (First or second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Current NCCN Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

NCCN information is current as of 2019-02-14. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

BRAF p.(V600E) c.1799T>A

cetuximab + vemurafenib + irinotecan

Cancer type: Colon Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Metachronus Metastatic Colon Cancer; Previous adjuvant FOLFOX/CAPEOX within past 12 months (Primary therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; If neither cetuximab or panitumumab previously given (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2018]

cetuximab + vemurafenib + irinotecan

Cancer type: Rectal Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Metachronous Metastatic Rectal Cancer; Previous adjuvant FOLFOX/CAPEOX within past 12 months (Primary therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; If neither cetuximab or panitumumab previously given (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 3.2018]

dabrafenib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; BRAF V600E mutation discovered prior to or during first-line systemic therapy if dabrafenib + trametinib is not tolerated (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression after first-line systemic therapy if dabrafenib + trametinib is not tolerated (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2019]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

dabrafenib + trametinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; BRAF V600E mutation discovered prior to or during first-line systemic therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression after first-line systemic therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2019]

dabrafenib + trametinib

Cancer type: Thyroid Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Anaplastic Carcinoma; Stage IVC; Aggressive therapy (Systemic therapy)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2018]

panitumumab + vemurafenib + irinotecan

Cancer type: Colon Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Metachronus Metastatic Colon Cancer; Previous adjuvant FOLFOX/CAPEOX within past 12 months (Primary therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; If neither cetuximab or panitumumab previously given (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2018]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

panitumumab + vemurafenib + irinotecan

Cancer type: Rectal Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Metachronous Metastatic Rectal Cancer; Previous adjuvant FOLFOX/CAPEOX within past 12 months (Primary therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; If neither cetuximab or panitumumab previously given (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 3.2018]

vemurafenib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; BRAF V600E mutation discovered prior to or during first-line systemic therapy if dabrafenib + trametinib is not tolerated (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression after first-line systemic therapy if dabrafenib + trametinib is not tolerated (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2019]

binimetinib + encorafenib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma (First-line therapy) (Preferred if clinically needed for early response)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

cobimetinib + vemurafenib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma (First-line therapy) (Preferred if clinically needed for early response)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

dabrafenib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF-inhibitor monotherapy with dabrafenib or vemurafenib are recommended options, especially when checkpoint immunotherapy is not appropriate (First-line therapy) (Preferred if clinically needed for early response)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

dabrafenib + trametinib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma (First-line therapy) (Preferred if clinically needed for early response)
- Resectable or Recurrent Cutaneous Melanoma (Adjuvant therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

vemurafenib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF-inhibitor monotherapy with dabrafenib or vemurafenib are recommended options, especially when checkpoint immunotherapy is not appropriate (First-line therapy) (Preferred if clinically needed for early response)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

binimetinib + encorafenib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy (Second-line or subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

cobimetinib + vemurafenib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy; if not used first line and not of same class (Second-line or subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

dabrafenib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF-inhibitor monotherapy with dabrafenib or vemurafenib are recommended options, especially when checkpoint immunotherapy is not appropriate (Second-line or subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

dabrafenib + trametinib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Cutaneous Melanoma; Initial or recurrent presentation; Microscopic satellite/in-transit disease; Post biopsy or surgery (Second-line, adjuvant, or recurrence therapy)
- Unresectable Cutaneous Melanoma (Therapy for recurrence)
- Metastatic Cutaneous Melanoma; Disseminated metastases (Therapy for metastatic disease)
- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy (Second-line or subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

vemurafenib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF-inhibitor monotherapy with dabrafenib or vemurafenib are recommended options, especially when checkpoint immunotherapy is not appropriate (Second-line or subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

dabrafenib

Cancer type: Thyroid Cancer **Variant class:** BRAF mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Papillary, Follicular, Hurthle Cell Carcinoma; CNS metastases or iodine-refractory bone metastases; Progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate (Not specified)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2018]

vemurafenib

Cancer type: Thyroid Cancer **Variant class:** BRAF mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Papillary, Follicular, Hurthle Cell Carcinoma; CNS metastases or iodine-refractory bone metastases; Progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate (Not specified)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2018]

vemurafenib

Cancer type: Melanoma **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Summary:

NCCN Guidelines® include the following supporting statement(s):
- "Although BRIM8 showed that adjuvant vemurafenib improved RFS and lowered risk of distant metastases relative to placebo, vemurafenib is not an FDA-approved adjuvant treatment option, and is not recommended by the NCCN Panel."

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

cetuximab

Cancer type: Colon Cancer **Variant class:** BRAF V600E mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2018]

cetuximab

Cancer type: Rectal Cancer **Variant class:** BRAF V600E mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 3.2018]

EGFR tyrosine kinase inhibitor

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600E mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "EGFR TKI therapy is not effective in patients with KRAS mutations, BRAF V600E mutations, ALK gene rearrangements, or ROS1 rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2019]

panitumumab

Cancer type: Colon Cancer **Variant class:** BRAF V600E mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2018]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

panitumumab

Cancer type: Rectal Cancer **Variant class:** BRAF V600E mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):

- "BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 3.2018]

trametinib

Cancer type: Melanoma **Variant class:** BRAF V600E mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "Although trametinib is FDA approved for single-agent use to treat patients with unresectable or metastatic melanoma with BRAF V600E mutation, trametinib monotherapy is no longer an NCCN recommended treatment option due to relatively poor efficacy compared with BRAF inhibitor monotherapy and BRAF/MEK inhibitor combination therapy."

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

dabrafenib + trametinib

Cancer type: Melanoma **Variant class:** BRAF V600 mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "As the COMBI-AD trial excluded patients with distant metastases, dabrafenib/trametinib is not a recommended adjuvant treatment option for resected stage IV disease."

Reference: NCCN Guidelines® - NCCN-Melanoma [Version 2.2019]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Current Clinical Trials Information

Clinical Trials information is current as of 2019-03-01. 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'.

BRAF p.(V600E) c.1799T>A

NCT02639546

A Phase I/II, Multicenter, Open-Label, Dose-Escalation Study of The Safety And Pharmacokinetics of Cobimetinib In Pediatric And Young Adult Patients With Previously Treated Solid Tumors

Cancer type: Glioblastoma

Variant class: RAS/RAF/MEK/ERK pathway

Other identifiers: 15-524, 16-041, 2015-0929, CTRC#15-0005, DRKS00010690, EudraCT Number: 2014-004685-25, GO29665, iMATRIX Cobi, iMATRIXcobi, IRAS ID: 174562, NCI-2016-00541, NL52503.078.16

Population segments: (N/A), Pediatric or Adolescent, Second line

Phase: I/II

Therapy: cobimetinib

Locations: Canada, France, Germany, Israel, Italy, Spain, United Kingdom, United States

US States: AZ, CA, FL, PA, TX

Contact: Reference Study ID Number: GO29665 [888-662-6728; global-roche-genentech-trials@gene.com]

NCT02693535

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

Cancer type: Unspecified Solid Tumor

Variant class: BRAF V600E mutation

Other identifiers: 20170529, NCI-2017-00510, Pro00014171, TAPUR

Population segments: (N/A), Aggressive, Diffuse large B-cell lymphoma (DLBCL), Extranodal marginal zone B-cell lymphoma (MALT), Follicular lymphoma (FL), Indolent, Lymphoblastic lymphoma (LBL), Mantle cell lymphoma (MCL), Other subtype, Second line, Small lymphocytic lymphoma (SLL), Stage III, Stage IV, Waldenstrom's macroglobulinemia (WM)

Phase: II

Therapy: cobimetinib + vemurafenib

Location: United States

US States: AL, AZ, CA, FL, GA, IL, MI, NC, ND, NE, OK, OR, PA, SD, TX, UT, VA, WA

Contact: Pam Mangat [pam.mangat@asco.org]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

NCT02091141

My Pathway: An Open-Label Phase IIa Study Evaluating Trastuzumab/ Pertuzumab, Erlotinib, Vemurafenib/ Cobimetinib, Vismodegib, Alectinib, and Atezolizumab in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

Cancer type: Unspecified Solid Tumor

Variant class: BRAF V600 mutation

Other identifiers: 1403013519, 2014-0459, AAAN9701, J1480, ML28897, ML28897/PRO 02, ML28897PRO/02, My Pathway, MyPathway, NCI-2014-01811, PRO 02

Population segments: BRCA, EGFR, Fourth line or greater, HER2 positive, Second line, Stage III, Stage IV, Third line

Exclusion criteria variant class: RAS mutation

Phase: II

Therapy: cobimetinib + vemurafenib

Location: United States

US States: AR, AZ, CA, CO, FL, GA, IL, MD, MN, MO, NC, ND, NY, OH, OK, OR, PA, SD, TN, TX, VA, WA, WI

Contact: Reference Study ID Number: ML28897 [888-662-6728; global-roche-genentech-trials@gene.com]

NCT03297606

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial

Cancer type: Unspecified Solid Tumor

Variant class: BRAF V600 mutation

Other identifiers: CA209-9DL, CAPTUR, ESR-17-12831, ML39800, PM1, WI233446

Population segments: Aggressive, Diffuse large B-cell lymphoma (DLBCL), Extranodal marginal zone B-cell lymphoma (MALT), First line, Follicular lymphoma (FL), Indolent, Lymphoblastic lymphoma (LBL), Mantle cell lymphoma (MCL), Other subtype, Second line, Stage III, Stage IV, Waldenstrom's macroglobulinemia (WM)

Phase: II

Therapy: cobimetinib + vemurafenib

Location: Canada

NCT02925234

A Dutch National Study on behalf of the Center for Personalized Cancer Treatment (CPCT) to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile

Cancer type: Unspecified Solid Tumor

Variant class: BRAF mutation

Other identifiers: DRUP, EudraCT Number: 2015-004398-33, M15DRU, NL54757.031.16

Population segments: Aggressive, Diffuse large B-cell lymphoma (DLBCL), First line, Follicular lymphoma (FL), Indolent, Mantle cell lymphoma (MCL), Other subtype, Second line, Small lymphocytic lymphoma (SLL), Stage III, Stage IV, Waldenstrom's macroglobulinemia (WM)

Phase: II

Therapies: cobimetinib + vemurafenib, dabrafenib

Location: Netherlands

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

NCT03520075
A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: RAS/RAF/MEK/ERK pathway

Other identifier: ASTX029-01

Population segments: Second line, Stage III, Stage IV

Phase: I/II

Therapy: ASTX029

Location: United States

US States: CT, TX, VA

Contact: Richard J. Morishige [925-560-2882; Richard.Morishige@astx.com]

NCT03781219
A Phase I, Single Arm, Dose Escalation Study to Evaluate Safety, Pharmacokinetics and Preliminary Efficacy of HL-085 Plus Vemurafenib in Patients With BRAF V600 Mutant Advanced Solid Tumor

Cancer type: Unspecified Solid Tumor

Variant class: BRAF V600 mutation

Other identifiers: CTR20180314, HL-085-102

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

Other inclusion criteria: ALK fusion negative, EGFR mutation negative

Phase: I

Therapy: HL-085 + vemurafenib

Location: China

NCT03118817
A Single-arm, Open-label, Multi-center, Phase I Expansion Study Evaluating the Efficacy and Safety of HM95573 Monotherapy in Patients With BRAF, KRAS or NRAS Mutation-positive Solid Cancers

Cancer type: Unspecified Solid Tumor

Variant class: BRAF mutation

Other identifier: HM-RAFI-102

Population segments: (N/A), Line of therapy N/A

Phase: I

Therapy: belvarafenib

Location: Republic of Korea

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

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, With an Expansion to Explore Intermittent Dosing in Combination With Everolimus

Cancer type: Unspecified Solid Tumor

Variant class: BRAF mutation

Other identifiers: CCR3808, DDU RAF/MEK, EudraCT Number: 2012-001040-22, IRAS ID:102403

Population segments: Adenocarcinoma, Fourth line or greater, KRAS, Second line, Stage III, Stage IV, Third line

Phase: I

Therapies: everolimus + RO-5126766, RO-5126766

Location: United Kingdom

NCT03051035

A Phase I First-in-Human Study of KO-947 in Locally Advanced Unresectable or Metastatic, Relapsed and/or Refractory Non-Hematological Malignancies

Cancer type: Unspecified Solid Tumor

Variant class: BRAF mutation

Other identifiers: 16-1101, 17-150, KO-ERK-001

Population segments: KRAS, Second line, Stage III, Stage IV

Phase: I

Therapy: KO-947

Location: United States

US State: PA

Contact: Kamn Lacroix [617-251-6535; medicalaffairs@kuraoncology.com]

NCT03634982

A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: BRAF mutation

Other identifiers: 19683, NCI-2018-02064, RMC-4630-01, UCI-18-14

Population segments: Second line, Stage III, Stage IV

Phase: I

Therapy: RMC-4630

Location: United States

US States: AZ, CA, CO, FL, OK, TN

Contact: Revolution Medicines [650-779-2300; CT-Inquiries@RevolutionMedicines.com]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

BRAF p.(V600E) c.1799T>A (continued)

NCT03284502
A Phase Ib, Open-label, Multicenter, Dose Escalation Study of the Safety, Tolerability, and Pharmacokinetics of Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: RAF mutation

Other identifier: HM-RAFI-103

Population segments: First line, Second line, Stage III, Stage IV

Phase: I

Therapy: belvarafenib + cobimetinib

Location: Republic of Korea

NCT02857270
A Phase I Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer

Cancer type: Unspecified Solid Tumor

Variant class: RAS/RAF/MEK/ERK pathway

Other identifiers: 16419, EudraCT Number: 2016-001907-21, I8S-MC-JUAB, JUAB, NCI-2017-00039

Population segments: Second line, Stage III, Stage IV

Phase: I

Therapies: abemaciclib + LY3214996 , LY3214996 , LY3214996 + chemotherapy, LY3214996 + midazolam

Locations: Australia, France, United States

US States: FL, MA, TN, TX

Contact: Eli Lilly and Company [877-285-4559]

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: 16-225, 2015-0913, CLXH254X2101, EudraCT Number: 2015-003421-33, NCI-2015-02280, NL55506.078.15, Nov RAFi (CLXH254X2101), REec-2016-2132, SNCTP000002708

Population segments: Second line, Stage III, Stage IV

Phase: I

Therapies: LXH254 , LXH254 + spartalizumab

Locations: Canada, France, Germany, Japan, Netherlands, Republic of Korea, Spain, Switzerland, United States

US States: NY, TX

Contact: Novartis Pharmaceuticals [888-669-6682; Novartis.email@novartis.com]

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

PIK3CB p.(L1049R) c.3146T>G

NCT02576444

A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD6738 in Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: PI3K/AKT/MTOR pathway

Other identifiers: 1508016363, 16-314, NCI-2016-00922, OLAPCO, VICCMD1672

Population segments: First line, Second line, Stage IV

Phase: II

Therapy: capivasertib + olaparib

Location: United States

US States: CT, MA, OH, TN

Contact: Manuel Avedissian [203-737-3669; manuel.avedissian@yale.edu]

NCT03673787

Ice-CAP: A Phase I Trial of Ipatasertib in Combination With Atezolizumab in Patients With Advanced Solid Tumours With PI3K Pathway Hyperactivation

Cancer type: Unspecified Solid Tumor

Variant class: PI3K/AKT/MTOR pathway

Other identifiers: CCR4720, EudraCT Number: 2017-003005-18, Ice-CAP, IceCAP, IRAS ID 233461

Population segments: Hormone refractory, Second line, Stage III, Stage IV

Phase: I/II

Therapy: atezolizumab + ipatasertib

Location: United Kingdom

NCT01884285

A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Anti-tumour Activity of AZD8186 in Patients with Advanced Castration-resistant Prostate Cancer (CRPC), Squamous Non-Small Cell Lung Cancer (sqNSCLC), Triple Negative Breast Cancer (TNBC) and Patients with Known PTEN-deficient/mutated or PIK3CB mutated/ amplified Advanced Solid Malignancies as Monotherapy and in Combination with Abiraterone Acetate or AZD2014

Cancer type: Unspecified Solid Tumor

Variant class: PIK3CB mutation

Other identifiers: 13-300, 20131275, 2015-057, AZD8186 study 1, D4620C00001, EudraCT Number: 2013-000703-17, IRAS ID: 129536, NCI-2013-02191, UW13043

Population segments: HER2 negative, Hormone refractory, Second line, Squamous Cell, Stage III, Stage IV, Triple receptor negative

Phase: I

Therapies: AZD8186, AZD8186 + abiraterone acetate + steroid, AZD8186 + vistusertib

Locations: Canada, Spain, United Kingdom, United States

US States: MA, MI, NY, WA, WI

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

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

PIK3CB p.(L1049R) c.3146T>G (continued)

NCT03065062

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

Cancer type: Unspecified Solid Tumor

Variant class: PI3K/AKT/MTOR pathway

Other identifiers: 16-499, NCI-2017-00434

Population segments: Second line, Squamous Cell, Stage III, Stage IV

Phase: I

Therapy: gedatolisib + palbociclib

Location: United States

US State: MA

Contact: Dr. Nicole Chau [617-632-3090]

NCT02389842

PIPA: A Phase Ib Study to Assess the Safety, Tolerability and Efficacy of the PI3K Inhibitors, Taselisib (GDC-0032) or Pictilisib (GDC-0941), in Combination With PAlbociclib, With the Subsequent Addition of Fulvestrant in PIK3CA-mutant Breast Cancers

Cancer type: Unspecified Solid Tumor

Variant class: PI3K/AKT/MTOR pathway

Other identifiers: CCR4191, EudraCT Number: 2014-002658-37, IRAS ID:159997, PIPA

Population segments: Estrogen receptor positive, Fourth line or greater, HER2 negative, HER2 positive, KRAS, Stage III, Stage IV, Triple receptor negative

Phase: I

Therapies: palbociclib + pictilisib, palbociclib + taselisib

Location: United Kingdom

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

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.

BRAF p.(V600E) c.1799T>A

Variant Class	Evidence Items
RAS/RAF/MEK/ERK pathway	4
↳ RAS/RAF/MEK/ERK mutation	0
↳ RAF mutation	1
↳ BRAF mutation status	0
↳ BRAF mutation	7
↳ BRAF activating mutation	0
↳ BRAF V600 mutation status	0
↳ BRAF V600 mutation	17
↳ BRAF V600E mutation status	0
↳ BRAF V600E mutation	27
↳ RAF aberration	0
↳ BRAF aberration	0
↳ BRAF mutation status	0
↳ BRAF mutation	7
↳ BRAF activating mutation	0
↳ BRAF V600 mutation status	0
↳ BRAF V600 mutation	17
↳ BRAF V600E mutation status	0
↳ BRAF V600E mutation	27
↳ RAF mutation	1
↳ BRAF mutation status	0
↳ BRAF mutation	7
↳ BRAF activating mutation	0
↳ BRAF V600 mutation status	0

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

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.

BRAF p.(V600E) c.1799T>A (continued)

Variant Class	Evidence Items
↳ BRAF V600 mutation	17
↳ BRAF V600E mutation status	0
↳ BRAF V600E mutation	27

PIK3CB p.(L1049R) c.3146T>G

Variant Class	Evidence Items
PI3K/AKT/MTOR pathway	4
↳ PIK3CB mutation	1

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Allele Frequency	Transcript	Variant Effect	Gene Class	Variant Class
PIK3CB	p.(L1049R)	c.3146T>G	COSM3408280	17.03%	NM_006219.2	missense	Gain of Function	Hotspot
BRAF	p.(V600E)	c.1799T>A	COSM476	14.50%	NM_004333.4	missense	Gain of Function	Hotspot

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

References

1. Kaanders et al. Pimonidazole binding and tumor vascularity predict for treatment outcome in head and neck cancer. Cancer Res. 2002 Dec 1;62(23):7066-74. PMID: 12460928
2. Cheng et al. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. Mod. Pathol. 2018 Jan;31(1):24-38. PMID: 29148538
3. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014 Oct 23;159(3):676-90. PMID: 25417114
4. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
5. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7. PMID: 22810696
6. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
7. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
8. Wan et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell. 2004 Mar 19;116(6):855-67. PMID: 15035987
9. Tiacci et al. BRAF mutations in hairy-cell leukemia. N. Engl. J. Med. 2011 Jun 16;364(24):2305-15. PMID: 21663470
10. Diamond et al. Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms. Cancer Discov. 2016 Feb;6(2):154-65. doi: 10.1158/2159-8290.CD-15-0913. Epub 2015 Nov 13. PMID: 26566875
11. Imielinski et al. Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma. J Clin Invest. 2014 Apr;124(4):1582-6. doi: 10.1172/JCI72763. Epub 2014 Feb 24. PMID: 24569458
12. Ciampi et al. Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. J. Clin. Invest. 2005 Jan;115(1):94-101. PMID: 15630448
13. Palanisamy et al. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. Nat. Med. 2010 Jul;16(7):793-8. PMID: 20526349
14. Jones et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res. 2008 Nov 1;68(21):8673-7. PMID: 18974108
15. Cin et al. Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma. Acta Neuropathol. 2011 Jun;121(6):763-74. doi: 10.1007/s00401-011-0817-z. Epub 2011 Mar 20. PMID: 21424530
16. Ross et al. The distribution of BRAF gene fusions in solid tumors and response to targeted therapy. Int. J. Cancer. 2016 Feb 15;138(4):881-90. PMID: 26314551
17. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202429s016lbl.pdf
18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202806s010lbl.pdf
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210496s001lbl.pdf
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204114Orig1s009lbl.pdf
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210498lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206192s002lbl.pdf
23. Villanueva et al. Concurrent MEK2 mutation and BRAF amplification confer resistance to BRAF and MEK inhibitors in melanoma. Cell Rep. 2013 Sep 26;4(6):1090-9. PMID: 24055054
24. Shi et al. Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. Cancer Discov. 2014 Jan;4(1):80-93. PMID: 24265155
25. Rizos et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. Clin. Cancer Res. 2014 Apr 1;20(7):1965-77. PMID: 24463458

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

References (continued)

26. Kulkarni et al. BRAF Fusion as a Novel Mechanism of Acquired Resistance to Vemurafenib in BRAFV600E Mutant Melanoma. Clin. Cancer Res. 2017 Sep 15;23(18):5631-5638. PMID: 28539463
27. Johnson et al. Acquired BRAF inhibitor resistance: A multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. Eur. J. Cancer. 2015 Dec;51(18):2792-9. PMID: 26608120
28. Nazarian et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature. 2010 Dec 16;468(7326):973-7. doi: 10.1038/nature09626. Epub 2010 Nov 24. PMID: 21107323
29. Shi et al. A novel AKT1 mutant amplifies an adaptive melanoma response to BRAF inhibition. Cancer Discov. 2014 Jan;4(1):69-79. PMID: 24265152
30. Van et al. The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. Cancer Discov. 2014 Jan;4(1):94-109. doi: 10.1158/2159-8290.CD-13-0617. Epub 2013 Nov 21. PMID: 24265153

Disclaimer: The data presented here is a result of the curation of published data sources, but may not be exhaustive. The data version is 2019.06(005).

Quality Metric	Controlled parameters	Sample
Chip loading	≥60%	75%
Total reads	>45 million reads	55,825,327
Enrichment	100% ideal	94%
Clonal: Polyclonal ratio	Up to 55% polyclonal	25%
Low Quality	≤26% approximately.	32%
Usable reads	≥30%	51%
Aligned bases	≥80% Can be less if base coverage, and % reads on target is high	91%
Unaligned bases	≤20%	9%
Mean raw accuracy	This value should be as close to 100% as possible	99%
Overall read length histogram	Median read length 98-115bp for DNA only, 65-90bp RNA only, DNA & RNA 100bp ±20	109

DNA

Quality Metric	Controlled parameters	Sample
Number of mapped reads	>4.5 million	7,495,462
Percent reads on target	>90%	93.78%
Average base coverage depth	>1200	2,058
Uniformity of amplicon (base) coverage	>90% (degraded 85-90%)	94.03%
Percent assigned amplicon reads	>90%	93.78%
Amplicons with no strand bias	>90%	95.48%
Amplicons reading end to end	>80%	93.04%
% base reads on target	>85%	91.04%
coverage at 1X	>90% coverage is required at 500X for samples with tumour percentages below 40%	99.97%
coverage at 20X		99.65%
coverage at 100X		98.77%
coverage at 500X		90.92%
MAPD value	In the presence of a copy number variant, this value should be <0.5	0.318

RNA

Quality Metric	Controlled parameters	Test specific figures
Mapped reads	>40,000 for software to call a fusion, (should be over 500,000)	463,842
Expression Control Genes MYC	>15 read counts indicates the gene is present (5 out of 6 genes should be present to accept the presence of a fusion)	1201
Expression Control Genes HMBS		108
Expression Control Genes TBP		143113
Expression Control Genes LRP1		53028
Expression Control Genes ITGB7		1767
Expression Control Genes MRPL13		50273

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

+44 (0) 1223 785 327 - info@oncologica.com

Ireland

Bymac Centre, Northwest
Business Park, Blanchardstow, Dublin 15

+353 1 8604204

Italy

Parco Tecnologico della Sardegna
Pula, Località Piscinamanna

+39 02 808 88210

Medical Laboratory
Accredited to ISO15189:2012

UKAS MEDICAL 9376

oncologica®

Leading a new era of precision oncology

Immunofocus®

PD-1/PD-L1 TESTING

IMMUNOFOCUS® TEST REPORT

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

Tel: +44(0)1223 785327
Email: info@oncologica.com

oncologica
Leading a new era of precision oncology

ONC19			
Surname		**Requester**	
Forename		**Contact details**	
DOB		**Date requested**	
Gender	Male		
Histology #		**Tumour %**	90%
Primary site	Primary Brain Tumour	**Tumour %**	-
Tumour subtype	Glioblastoma	**(macrodissected)**	
Tissue Type	Posterio/inferior Brain Tumour		

PD-L1 test

PD-L1 IHC assays are used to help identify those patients most likely to benefit from anti-PD-1/PD-L1 directed immunotherapies. Assessment involves the determination of a range of cut-off/threshold values for PD-L1 positive tumour cells and PD-L1 positive immune cells. These cut off values are identified as predictors of response to anti-PD-L1 directed therapies used in the treatment of a range of different cancer types and include pembrolizumab, atezolizumab, avelumab, nivolumab, and durvalumab. The established cut off values for tumour proportion scores (>1%, >25%, >50%) and PD-L1 positive immune cells (10%), which vary according to immunotherapy, tumour type and whether first or second line therapy is to be used.

The Oncologica® Immunofocus PD-L1 immunocytochemistry assay quantifies the proportion of tumour cells that express PD-L1 (Tumour Proportion Score) and the area occupied by tumour infiltrating PD-L1 positive immune cells.

The Oncologica® Immunofocus PD-L1 immunocytochemistry assay is a Laboratory Developed Test utilising the RUO rabbit monoclonal antibody clone E1L3N (Cell Signalling Technologies) and Leica Bond III instrumentation. The performance of the Immunofocus assay is continually assessed by involvement in recognised External Quality Assessment schemes and returns performance levels commensurate with approved the PD-L1 diagnostic assays. All Immunofocus assay testing is performed within the scope of UKAS/ISO 15189:2012 accreditation. Clone E1L3N is not licensed and approved for use in clinical testing to direct the use of PD-1/PD-L1 therapies. The PD-L1 protein expression levels in tumour cells generated by the Immunofocus PD-L1 assay should therefore be interpreted within the context of these facts.

PD-L1 Result

The tumour shows markedly high expression levels of PD-L1. The majority of tumour cells show strong or moderate intensity immunostaining for PD-L1 with complete patterns of surface membrane expression. The proportion of PD-L1 expressing tumour cells amounts to around 85-90% of the total tumour cell population. The tumour is associated with a focal sparse PD-L1 expressing immune cell (IC) infiltrate. The PD-L1 expressing tumour infiltrating immune cells (ICs) cover <1% of the tumour area occupied by tumour cells, intratumoural and contiguous peritumoural stroma.

Summary; PD-L1 Tumour Proportion Score 85-90%; PD-L1 positive ICs <1% of tumour area

Oncologica UK Ltd, Suite 2, The Newnham Building,
Chesterford Research Park, Little Chesterford,
Cambridge, CB10 1XL

+44 (0) 1223 785 327 - info@oncologica.com

Ireland

Bymac Centre, Northwest
Business Park, Blanchardstow, Dublin 15

+353 1 8604204

Italy

Parco Tecnologico della Sardegna
Pula, Località Piscinamanna

+39 02 808 88210