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Leading a new era of precision oncology

Oncofocus®

Precision Oncology

ONCOFOCUS® TEST REPORT

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Lead Clinical Scientist: - **Clinical Scientist:** -

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Patient demographics

ONC19	-		
Surname	-	**Requester**	-
Forename	-	**Contact details**	-
DOB	-	**Date requested**	-
Gender	-		
Histology #	-	**Tumour %**	>95%
Primary site	Brain	**Tumour % (macrodissected)**	-
Tumour subtype	Glioblastoma		
Tissue Type	Right Temporal 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 10, the NCT numbers are hyperlinks to the clinicaltrials.gov webpages which should be accessed to gain further trial specific information

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Clinically Significant Biomarkers

Indicated **Contraindicated**

Genomic Alteration		Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
PTEN p.(G251D) c.752G>A	47%	Clinical trials and/or off-label	Clinical trials and/or off-label	13
PIK3R1 p.(N564D) c.1690A>G	18%	Clinical trials and/or off-label	Clinical trials and/or off-label	7
NF1 p.(Q236) c.706C>T*	40%	Clinical trials and/or off-label	Clinical trials and/or off-label	7
MLH1 p.(Q301) c.901C>T*	28%	Clinical trials and/or off-label	Clinical trials and/or off-label	6
IDH1 p.(R132H) c.395G>A	41%	Clinical trials and/or off-label	Clinical trials and/or off-label	4
CDKN2A deletion; copy number 0.24		Clinical trials and/or off-label	Clinical trials and/or off-label	4
CDKN2B deletion; copy number 0.21		Clinical trials and/or off-label	Clinical trials and/or off-label	2
TP53 p.(R273C) c.817C>T *p.(H214L) c.641A>T*	40% 42%	Clinical trials and/or off-label	Clinical trials and/or off-label	1

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.

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Biomarker Descriptions

IDH1 (isocitrate dehydrogenase (NADP(+)) 1, cytosolic)

Background: The IDH1 and IDH2 genes encode homologous isocitrate dehydrogenase enzymes that catalyze the conversion of isocitrate to α-ketoglutarate (α-KG)[1]. The IDH1 gene encodes the NADP+ dependent cytoplasmic isocitrate dehydrogenase enzyme; IDH2 encodes the mitochondrial isoform.

Alterations and prevalence: Recurrent somatic mutations in IDH1 and IDH2 are mutually exclusive and observed in several malignancies including glioma, chondrosarcoma, intrahepatic cholangiocarcinoma, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS)[2]. Recurrent IDH1 variants include predominately R132H/C plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity[3]. Although wild-type enzymatic activity is ablated, recurrent IDH1 variants catalyze the conversion of α-KG to D-2-hydroxyglutarate, an oncometabolite with diverse effects on cellular metabolism, epigenetic regulation, redox states, and DNA repair[1,4]. Recurrent IDH1 mutations are present in 5-10% of patients with AML and 5% of patients with MDS[5,6,7]. Recurrent IDH1 mutations are present in nearly 80% of lower grade diffuse gliomas[8,9].

Potential clinical relevance: Ivosidenib[10] is FDA approved (2018) for the treatment of AML patients with IDH1 R132C/G/H/L/S variants[11]. IDH1 mutations are associated with poor prognosis in primary myelofibrosis[12] but have been shown to confer improved prognosis in lower grade gliomas[13,14].

PTEN (phosphatase and tensin homolog)

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[15]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[16,16,17]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[18]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[19].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer[8,9]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[17,20,21,22,23]. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer[8,9].

Potential clinical relevance: Currently, no therapies are approved for PTEN aberrations. However, due to the role of PTEN in genome stability, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[24,25].

TP53 (tumor protein p53)

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[26]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[27,28].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[8,9,29,30,31,32]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, R248, R273, and R282[8,9]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[33,34,35,36].

Potential clinical relevance: Currently, no targeted therapies are approved for TP53 aberrations. TP53 mutations confer poor prognosis in acute myeloid leukemias, as well as myelodysplastic syndromes and myeloproliferative neoplasms[12,37,38]. Several investigational therapies including drugs aimed at restoring wild type p53 activity, affecting downstream targets, or compounds that induce synthetic lethality are under clinical evaluation39,40.

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Tier Criteria Met

Genomic Alteration	Tier Classification for Glioblastoma
PTEN mutation Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
PIK3R1 mutation Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
NF1 mutation Tier: IIC	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
MLH1 mutation Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
IDH1 mutation Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
CDKN2A deletion Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
CDKN2B deletion Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
TP53 mutation 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

PTEN mutation

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
capivasertib + olaparib	✖	✖	✖	✖	● (II)
everolimus	✖	✖	✖	✖	● (II)
everolimus + ribociclib	✖	✖	✖	✖	● (II)
niraparib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
temsirolimus	✖	✖	✖	✖	● (II)
atezolizumab + ipatasertib	✖	✖	✖	✖	● (I/II)

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

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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

PTEN mutation (continued)

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
ARQ-751	✖	✖	✖	✖	● (I)
AZD8186 + chemotherapy	✖	✖	✖	✖	● (I)
AZD8186, AZD8186 + abiraterone acetate + steroid, AZD8186 + vistusertib	✖	✖	✖	✖	● (I)
gedatolisib + palbociclib	✖	✖	✖	✖	● (I)
palbociclib + pictilisib, palbociclib + taselisib	✖	✖	✖	✖	● (I)

PIK3R1 mutation

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
capivasertib + olaparib	✖	✖	✖	✖	● (II)
everolimus	✖	✖	✖	✖	● (II)
everolimus + ribociclib	✖	✖	✖	✖	● (II)
temsirolimus	✖	✖	✖	✖	● (II)
atezolizumab + ipatasertib	✖	✖	✖	✖	● (I/II)
gedatolisib + palbociclib	✖	✖	✖	✖	● (I)
palbociclib + pictilisib, palbociclib + taselisib	✖	✖	✖	✖	● (I)

NF1 mutation

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
temsirolimus	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
cobimetinib	✖	✖	✖	✖	● (I/II)
abemaciclib + LY3214996 , LY3214996 , LY3214996 + chemotherapy, LY3214996 + midazolam	✖	✖	✖	✖	● (I)
everolimus + RO-5126766, RO-5126766	✖	✖	✖	✖	● (I)

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

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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

NF1 mutation (continued)

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
LXH254 , LXH254 + spartalizumab	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)

MLH1 mutation

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
atezolizumab	✖	✖	✖	✖	● (II)
pembrolizumab	✖	✖	✖	✖	● (II)
prexasertib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
BAY-1895344	✖	✖	✖	✖	● (I/II)
pamiparib + tislelizumab	✖	✖	✖	✖	● (I)

IDH1 mutation

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
niraparib	✖	✖	✖	✖	● (II)
nivolumab	✖	✖	✖	✖	● (II)
veliparib + chemotherapy, veliparib + radiation therapy	✖	✖	✖	✖	● (II)
ribociclib + trametinib	✖	✖	✖	✖	● (I)

CDKN2A deletion

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
everolimus + ribociclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)

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

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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

CDKN2B deletion

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
everolimus + ribociclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)

TP53 mutation

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
adavosertib + olaparib	✖	✖	✖	✖	● (II)

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

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Relevant Therapy Details

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.

NF1 mutation

imatinib

Cancer type: Gastrointestinal Stromal Tumor **Variant class:** NF1 mutation

Other criteria: BRAF wild type, KIT wild type, PDGFR wild type, SDH underexpression

ESMO Level of Evidence/Grade of Recommendation: IV / D

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:
- "With regard to so called KIT/PDGFRA/BRAFWT GIST, there is a consensus on avoiding adjuvant treatment in NF1-related and SDH expression-negative GISTs [IV, D]."

Reference: ESMO Clinical Practice Guidelines - ESMO-EUROCAN-Gastrointestinal Stromal Tumours [Ann Oncol (2018) 29 (Suppl 4): iv68–iv78.]

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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'.

PTEN mutation

NCT03834740
A Phase 0/II Study of Ribociclib (LEE011) in Combination With Everolimus in Preoperative Rb-Intact Recurrent High-Grade Glioma Patients Scheduled for Resection to Evaluate Central Nervous System (CNS) Penetration

Cancer type: Glioblastoma

Variant class: PTEN mutation

Other identifier: 18-500-311-70-38

Population segments: (N/A), Neoadjuvant, Second line

Exclusion criteria variant class: RB1 mutation

Phase: II

Therapy: everolimus + ribociclib

Location: United States

US State: AZ

Contact: Jocelyn Harmon [602-406-3246; jocelyn.harmon@dignityhealth.org]

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: PTEN mutation

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]

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: PTEN mutation

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

Population segments: Maintenance/Consolidation, Second line, Stage III, Stage IV, Third line

Phase: II

Therapy: everolimus

Location: France

PTEN mutation (continued)

NCT03207347
A Phase II Trial of the PARP Inhibitor, Niraparib, in BAP1 and Other DNA Damage Response (DDR) Pathway Deficient Neoplasms (UF-STO-ETI-001)

Cancer type: Unspecified Solid Tumor

Variant class: PTEN mutation

Other identifier: UF-STO-ETI-001

Population segments: (N/A), Second line

Phase: II

Therapy: niraparib

Location: United States

US State: FL

Contact: Ashton Monismith [352-265-0680 ext 87657; amonismith@ufl.edu]

NCT02286687
Phase II Study of the PARP Inhibitor BMN 673 (Talazoparib Tosylate) in Advanced Cancer Patients With Somatic Alterations in BRCA1/2, Mutations/Deletions in PTEN or PTEN Loss, a Homologous Recombination Defect, Mutations/ Deletions in Other BRCA Pathway Genes and Germline Mutation in BRCA1/2 (Not Breast or Ovarian Cancer)

Cancer type: Unspecified Cancer

Variant class: PTEN mutation

Other identifiers: 2013-0961, NCI-2014-02494

Population segments: Fourth line or greater, Stage III, Stage IV

Phase: II

Therapy: talazoparib

Location: United States

US State: TX

Contact: Dr. Sarina Piha-Paul [713-563-1930]

NCT02401347
A Phase II Clinical Trial of the PARP Inhibitor Talazoparib in BRCA1 and BRCA2 Wild-Type Patients With (i) Advanced Triple-Negative Breast Cancer and Homologous Recombination Deficiency, and (ii) Advanced HER2-Negative Breast Cancer or Other Solid Tumors With Either a Mutation in Homologous Recombination Pathway Genes Talazoparib Beyond BRCA (TBB) Trial

Cancer type: Unspecified Solid Tumor

Variant class: PTEN mutation

Other identifiers: BRS0050, NCI-2015-00036, TBB

Population segments: HER2 negative, Second line, Stage III, Stage IV, Triple receptor negative

Other inclusion criteria: BRCA1 germline mutation negative, BRCA2 germline mutation negative, ERBB2 negative

Exclusion criteria variant classes: BRCA1 deleterious mutation, BRCA2 deleterious mutation

Phase: II

Therapy: talazoparib

Location: United States

US State: CA

Contact: Pei Jen Chang [650-725-0866; peijenc@stanford.edu]

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PTEN mutation (continued)

NCT03297606
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial

Cancer type: Unspecified Solid Tumor

Variant class: PTEN aberration

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: temsirolimus

Location: Canada

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

NCT02761694
A Phase I Dose Escalation Study of ARQ 751 in Adult Subjects With Advanced Solid Tumors With AKT1, 2, 3 Genetic Alterations, Activating PI3K Mutations, PTEN-null, or Other Known Actionable PTEN Mutations

Cancer type: Unspecified Solid Tumor

Variant class: PTEN mutation

Other identifiers: 2016-0212, ARQ 751-101, NCI-2016-00913, PTEN-null

Population segments: Estrogen receptor positive, HER2 negative, Progesterone receptor positive, Second line, Stage III, Stage IV

Phase: I

Therapy: ARQ-751

Location: United States

US States: TN, TX

Contact: ArQule [781-994-0300; ClinicalTrials@arqule.com]

PTEN mutation (continued)

NCT03218826
A Phase I Study of AZD8186 in Combination With Docetaxel in Patients With PTEN Mutated or PIK3CB Mutated Advanced Solid Tumors, Potentially Amenable to Docetaxel

Cancer type: Unspecified Solid Tumor

Variant class: PTEN mutation

Other identifiers: 10131, 18-237, NCI10131, NCI-2017-01232

Population segments: Estrogen receptor positive, HER2 negative, Second line, Stage III, Stage IV, Triple receptor negative

Exclusion criteria variant classes: PIK3CA mutation, RAF mutation

Phase: I

Therapy: AZD8186 + chemotherapy

Location: United States

US States: MD, NY, TX

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

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: PTEN 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]

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]

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PTEN mutation (continued)

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

PIK3R1 mutation

NCT03834740
A Phase 0/II Study of Ribociclib (LEE011) in Combination With Everolimus in Preoperative Rb-Intact Recurrent High-Grade Glioma Patients Scheduled for Resection to Evaluate Central Nervous System (CNS) Penetration

Cancer type: Glioblastoma

Variant class: PIK3R1 mutation

Other identifier: 18-500-311-70-38

Population segments: (N/A), Neoadjuvant, Second line

Exclusion criteria variant class: RB1 mutation

Phase: II

Therapy: everolimus + ribociclib

Location: United States

US State: AZ

Contact: Jocelyn Harmon [602-406-3246; jocelyn.harmon@dignityhealth.org]

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: PIK3R1 mutation

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

Population segments: Maintenance/Consolidation, Second line, Stage III, Stage IV, Third line

Phase: II

Therapy: everolimus

Location: France

PIK3R1 mutation (continued)

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: PIK3R1 aberration

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]

NCT03297606
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial

Cancer type: Unspecified Solid Tumor

Variant class: PIK3R1 aberration

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: temsirolimus

Location: Canada

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

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PIK3R1 mutation (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

NF1 mutation

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]

NF1 mutation (continued)

NCT03297606
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial

Cancer type: Unspecified Solid Tumor

Variant class: NF1 aberration

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: temsirolimus

Location: Canada

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]

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: NF1 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]

NF1 mutation (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: RAS/RAF/MEK/ERK 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

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]

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MLH1 mutation

NCT02658279
A Proof-of-Concept, Pilot Study of Pembrolizumab (MK-3475) in Patients With Recurrent Malignant Glioma With a Hypermutator Phenotype

Cancer type: Glioblastoma

Variant class: MLH1 mutation

Other identifiers: 15-227, 16-530, 2016-0859, NCI-2016-00116

Population segments: (N/A), Second line

Phase: II

Therapy: pembrolizumab

Location: United States

US States: CA, FL, MA, NJ, NY, TX, UT

Contact: Dr. Thomas Kaley [212-639-5122]

NCT03767075
Basket of Baskets: A Modular, Open-label, Phase II, Multicentre Study To Evaluate Targeted Agents in Molecularly Selected Populations With Advanced Solid Tumours

Cancer type: Unspecified Solid Tumor

Variant class: MLH1 mutation

Other identifiers: (Basket of Baskets) (BoB), EudraCT number: 2017-005108-89, MO39164, VHIO17002

Population segments: Second line, Stage III, Stage IV

Phase: II

Therapy: atezolizumab

Locations: France, Spain

NCT02873975
A Phase II Study of the CHK1 Inhibitor LY2606368 in Patients With Advanced Solid Tumors Exhibiting Replicative Stress or Homologous Recombination Repair Deficiency

Cancer type: Unspecified Solid Tumor

Variant class: Fanconi anemia pathway

Other identifiers: 16-281, I4D-MC-E006, NCI-2016-01564

Population segments: Second line, Stage III, Stage IV

Phase: II

Therapy: prexasertib

Location: United States

US State: MA

Contact: Dr. Geoffrey Shapiro [617-632-4942; Geoffrey_Shapiro@dfci.harvard.edu]

MLH1 mutation (continued)

NCT02286687
Phase II Study of the PARP Inhibitor BMN 673 (Talazoparib Tosylate) in Advanced Cancer Patients With Somatic Alterations in BRCA1/2, Mutations/Deletions in PTEN or PTEN Loss, a Homologous Recombination Defect, Mutations/ Deletions in Other BRCA Pathway Genes and Germline Mutation in BRCA1/2 (Not Breast or Ovarian Cancer)

Cancer type: Unspecified Cancer

Variant class: Fanconi anemia pathway

Other identifiers: 2013-0961, NCI-2014-02494

Population segments: Fourth line or greater, Stage III, Stage IV

Phase: II

Therapy: talazoparib

Location: United States

US State: TX

Contact: Dr. Sarina Piha-Paul [713-563-1930]

NCT03188965
An Open-label, First-in-human, Dose-escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Maximum Tolerated Dose and / or Recommended Phase II Dose of the ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas

Cancer type: Unspecified Solid Tumor

Variant class: DNA repair pathway

Other identifiers: 18594, 2017-0186, BAY1895344/18594, EudraCT Number: 2016-004484-39, IRAS ID-218516, NCI-2018-00206, Trial ID: 16754

Population segments: Adenocarcinoma, Aggressive, Diffuse large B-cell lymphoma (DLBCL), Hormone refractory, Indolent, Mantle cell lymphoma (MCL), Second line, Squamous Cell, Stage III, Stage IV

Phase: I/II

Therapy: BAY-1895344

Locations: Canada, Singapore, Switzerland, United Kingdom, United States

US State: TX

Contact: Bayer Clinical Trials Contact [888-842-2937; clinical-trials-contact@bayer.com]

NCT02660034
A Phase I/Ib, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activity of the Anti-PD-1 Monoclonal Antibody BGB-A317 in Combination With the PARP Inhibitor BGB-290 in Subjects With Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: DNA repair mutation

Other identifiers: 16-183, 18-009, A317/290, BGB-A317/BGB-290, BGB-A317/ BGB-290_Study_001, CT783, NCI-2018-00791, P 55217, VICCPHI1814

Population segments: HER2 negative, Pulmonary, Second line, Stage III, Stage IV, Third line, Triple receptor negative

Phase: I

Therapy: pamiparib + tislelizumab

Locations: Australia, France, New Zealand, Spain, United Kingdom, United States

US States: AZ, CA, CO, FL, MA, NY, PA, TN, TX, VA

Contact: Rob Stewart [clinicaltrials@beigene.com]

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IDH1 mutation

NCT03557359
A Phase II, Open Label, Single Arm Study of Nivolumab for Recurrent or Progressive IDH Mutant Gliomas With Prior Exposure to Alkylating Agents

Cancer type: Glioblastoma

Variant class: IDH1 mutation

Other identifiers: AAAR6354, NCI-2018-02156

Population segments: (N/A), First line, Untreated

Phase: II

Therapy: nivolumab

Location: United States

US State: NY

Contact: Dr. Fabio Iwamoto [212-342-0571; fi2146@cumc.columbia.edu]

NCT03581292
A Phase II Study of Veliparib (ABT-888) and Local Irradiation, Followed by Maintenance Veliparib and Temozolomide, in Patients With Newly Diagnosed High-Grade Glioma (HGG) Without H3 K27M or BRAFV600E Mutations

Cancer type: Glioblastoma

Variant class: IDH1 mutation

Other identifiers: ACNS1721, NCI-2018-01361

Population segments: First line, Maintenance/Consolidation, Pediatric or Adolescent, Untreated

Other inclusion criteria: BRAF V600E mutation negative, H3F3A K27M mutation negative

Exclusion criteria variant classes: BRAF V600E mutation, H3F3A K27M mutation

Phase: II

Therapies: veliparib + chemotherapy, veliparib + radiation therapy

Location: United States

US States: AR, CT, FL, GA, IN, MA, MD, MO, MS, NC, ND, NV, OH, OK, OR, PA, TN, TX, VA

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

NCT03434262
Molecularly-Driven Doublet Therapy for All Children With Refractory or Recurrent CNS Malignant Neoplasms and Young Adults With Refractory or Recurrent SHH Medulloblastoma

Cancer type: Glioblastoma

Variant class: IDH mutation

Other identifiers: NCI-2018-00284, SJDAWN

Population segments: Pediatric or Adolescent, Second line

Exclusion criteria variant class: RB1 mutation

Phase: I

Therapy: ribociclib + trametinib

Location: United States

US State: TN

Contact: Tabatha E. Doyle [901-595-2544; tabatha.doyle@stjude.org]

IDH1 mutation (continued)

NCT03207347
A Phase II Trial of the PARP Inhibitor, Niraparib, in BAP1 and Other DNA Damage Response (DDR) Pathway Deficient Neoplasms (UF-STO-ETI-001)

Cancer type: Unspecified Solid Tumor

Variant class: IDH1 mutation

Other identifier: UF-STO-ETI-001

Population segments: (N/A), Second line

Phase: II

Therapy: niraparib

Location: United States

US State: FL

Contact: Ashton Monismith [352-265-0680 ext 87657; amonismith@ufl.edu]

CDKN2A deletion

NCT03834740
A Phase 0/II Study of Ribociclib (LEE011) in Combination With Everolimus in Preoperative Rb-Intact Recurrent High-Grade Glioma Patients Scheduled for Resection to Evaluate Central Nervous System (CNS) Penetration

Cancer type: Glioblastoma

Variant class: CDKN2A deletion

Other identifier: 18-500-311-70-38

Population segments: (N/A), Neoadjuvant, Second line

Exclusion criteria variant class: RB1 mutation

Phase: II

Therapy: everolimus + ribociclib

Location: United States

US State: AZ

Contact: Jocelyn Harmon [602-406-3246; jocelyn.harmon@dignityhealth.org]

NCT02693535
Targeted Agent and Profiling Utilization Registry (TAPUR) Study

Cancer type: Unspecified Solid Tumor

Variant class: CDKN2A deletion

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: palbociclib

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]

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CDKN2A deletion (continued)

NCT03297606
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial

Cancer type: Unspecified Solid Tumor

Variant class: CDKN2A aberration

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: palbociclib

Location: Canada

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, UPCC 03909, UPCC03909

Population segments: Estrogen receptor positive, Fourth line or greater, HER2 negative, HER2 positive, Metastatic, Progesterone receptor positive, Second line, Stage III, Stage IV, Third line, Triple receptor negative

Phase: II

Therapy: palbociclib

Location: United States

US State: PA

Contact: Dr. Peter O. Dwyer [855-216-0098; PennCancerTrials@emergingmed.com]

CDKN2B deletion

NCT03834740
A Phase 0/II Study of Ribociclib (LEE011) in Combination With Everolimus in Preoperative Rb-Intact Recurrent High-Grade Glioma Patients Scheduled for Resection to Evaluate Central Nervous System (CNS) Penetration

Cancer type: Glioblastoma

Variant class: CDKN2B deletion

Other identifier: 18-500-311-70-38

Population segments: (N/A), Neoadjuvant, Second line

Exclusion criteria variant class: RB1 mutation

Phase: II

Therapy: everolimus + ribociclib

Location: United States

US State: AZ

Contact: Jocelyn Harmon [602-406-3246; jocelyn.harmon@dignityhealth.org]

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CDKN2B deletion (continued)

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, UPCC 03909, UPCC03909

Population segments: Estrogen receptor positive, Fourth line or greater, HER2 negative, HER2 positive, Metastatic, Progesterone receptor positive, Second line, Stage III, Stage IV, Third line, Triple receptor negative

Phase: II

Therapy: palbociclib

Location: United States

US State: PA

Contact: Dr. Peter O. Dwyer [855-216-0098; PennCancerTrials@emergingmed.com]

TP53 mutation

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: TP53 mutation

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

Population segments: First line, Second line, Stage IV

Phase: II

Therapy: adavosertib + olaparib

Location: United States

US States: CT, MA, OH, TN

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

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Lead Clinical Scientist: - **Clinical Scientist:** -

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.

PTEN mutation

Variant Class	Evidence Items
PI3K/AKT/MTOR pathway	6
↳ PTEN aberration	1
↳ PTEN mutation	9

PIK3R1 mutation

Variant Class	Evidence Items
PI3K/AKT/MTOR pathway	6
↳ PIK3R1 aberration	2
↳ PIK3R1 mutation	2

NF1 mutation

Variant Class	Evidence Items
RAS/RAF/MEK/ERK pathway	4
↳ NF1 aberration	1
↳ NF1 mutation	2
↳ RAS/RAF/MEK/ERK mutation	1
↳ NF1 mutation	2

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Lead Clinical Scientist: - **Clinical Scientist:** -

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.

MLH1 mutation

Variant Class	Evidence Items
DNA repair pathway	1
↳ DNA repair mutation	1
↳ MLH1 mutation	2
MMR pathway	0
↳ MMR mutation pathway	0
↳ MLH1 mutation	2
Fanconi anemia pathway	2
↳ MLH1 mutation	2

IDH1 mutation

Variant Class	Evidence Items
IDH mutation	1
↳ IDH1 mutation	3

CDKN2A deletion

Variant Class	Evidence Items
G1/S cell cycle pathway	2
↳ CDKN2A aberration	1
↳ CDKN2A negative	0
↳ CDKN2A deletion	2

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Lead Clinical Scientist: - **Clinical Scientist:** -

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.

CDKN2B deletion

Variant Class	Evidence Items
G1/S cell cycle pathway	2
↳ CDKN2B deletion	1

TP53 mutation

Variant Class	Evidence Items
TP53 aberration	0
↳ TP53 mutation	1

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Immunofocus®

PD-1/PD-L1 TESTING

IMMUNOFOCUS® TEST REPORT

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ONC19			
Surname		**Requester**	
Forename		**Contact details**	
DOB		**Date requested**	
Gender	Female		
Histology #		**Tumour %**	>95%
Primary site	Brain	**Tumour %**	-
Tumour subtype	Glioblastoma	**(macrodissected)**	
Tissue Type	Right Temporal 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 a heterogeneous pattern of PD-L1 expression. In some focal areas a significant proportion (30%) of tumour cells show moderate or weak intensity immunostaining for PD-L1 with partial and complete patterns of surface membrane expression. However the majority of tumour cells show absence of PD-L1 expression. Taken together the proportion of PD-L1 expressing tumour cells amounts to <1% of the total tumour cell population. The tumour is associated with a diffusely distributed PD-L1 expressing immune cell (IC) infiltrate. 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 <1% ; PD-L1 positive ICs <1% of tumour area

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[IHC testing - MMR] Patient Test Report

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ONC19			
Surname		**Requester**	
Forename		**Contact details**	
DOB		**Date requested**	
Gender	Female		
Histology #		**Tumour %**	>95%
Primary site	Brain	**Tumour %**	-
Tumour subtype	Glioblastoma	**(macrodissected)**	
Tissue Type	Right Temporal Tumour		

MMR test report

The tumour was immunostained for the four MMR proteins MLH1, MSH2, MSH6 and PMS2. Immunostaining of tumour cell nuclei was observed for MLH1, MSH2 and MSH6. However a complete absence of nuclear immunoexpression was observed for PMS2. This contrasts with high expression levels of PMS2 in control tissues and intratumoural immune cells (ICs). The loss of MMR proteins is an indicator of mismatch repair (MMR) deficiency.

Summary: Evidence of abnormal MMR expression by IHC has been identified indicative of MisMatch Repair (MMR) deficiency. The FDA has approved pembrolizumab for MMR deficient solid tumours that have progressed following prior treatment and have no satisfactory alternative treatment options.

Immunohistochemistry was performed by UCL-AD London. The Pathological interpretation of results was performed at Oncologica UK Ltd.

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[TMB] Patient Test Report

Predictive testing for Immunotherapy

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Lead Clinical Scientist: Keeda Hardisty

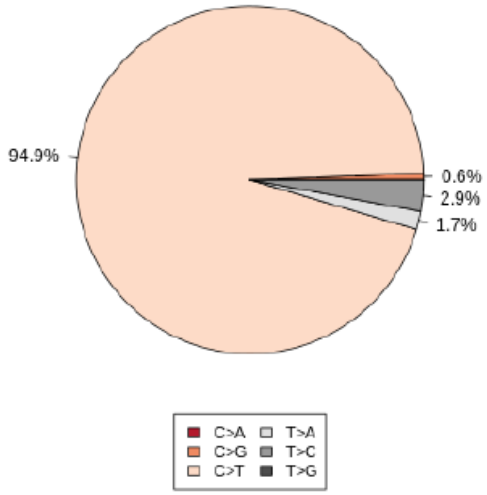
Date:

Tumour Mutation Burden (TMB) Status: 106.75 Mutations/MB

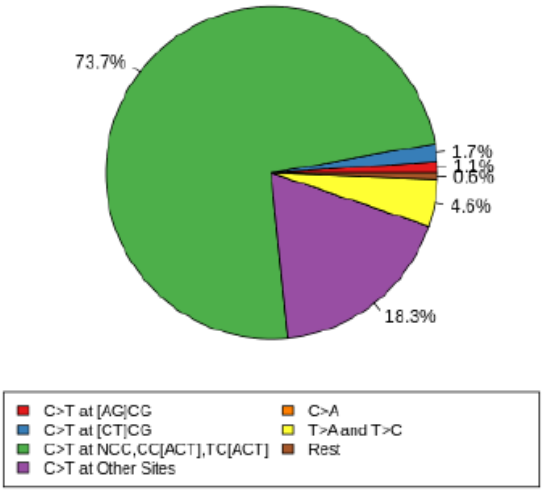
QC Metrics

Average Coverage	Total Variants Called	Estimated SNP proportion consistent with Deamination (mainly FFPE)	Mean depth	Uniformity
841.0	1,142	6	841.5	94.85%

Substitution Type of Somatic Mutations



Signature Pattern of Somatic Mutations



Additional Information:

High C>T at CpG is consistent with Spontaneous deamination of 5-methylcytosine[1]

High C>T at CpC, CpC, TpC, T>A, and T>C is consistent with UV damage[2]

High C>A is consistent with smoking damage[3]

High C>T (site independent) is consistent with FFPE processing[4]

[1] Alexandrov LB et al. *Nature*. 2013;[2]Hayward NK et al. Nature. 2017; [3]Alexandrov LB et al. *Cancer Etiology*. 2016;[4]Wong SQ et al. *BMC Medical Genomics*. 2014;

ONC19-:
Referring pathology dept: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