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

Patient demographics

ONC20	-		
Surname	-	**Requester**	-
Forename	-	**Contact details**	-
DOB	-	**Date requested**	-
Gender	Female		
Histology #	-	**Tumour %**	70%
Primary site	Right Eye	**Tumour %**	-
Tumour subtype	Spindle Cell Melanoma	**(macrodissected)**	
Tissue Type	Endorescection Right Eye		

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 738 anti-cancer targeted therapies/therapy combinations.

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

In addition to the variants listed below, a pathogenic variant in the SF3B1 gene was also detected, c.1874G>A, p.(Arg625His), however at this time it does not link to any therapies/clinical trials.

Within the 'Current Clinical Trials Information' section of this report, starting on page 7, the NCT numbers are hyperlinks to the clinicaltrials.gov webpages which should be accessed to gain further trial specific information

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	Alt Allele Freq	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
GNA11 mutation *c.626A>T, p.(Gln209Leu)*	42.26%	Clinical trials and/or off-label	Clinical trials and/or off-label	9
BAP1 mutation *c.1366C>T, p.(Gln456Ter)*	72.81%	Clinical trials and/or off-label	Clinical trials and/or off-label	7
FANCD2 deletion *(copy number = 0.63)*		Clinical trials and/or off-label	Clinical trials and/or off-label	5
ATR deletion *(copy number = 0.76)*		Clinical trials and/or off-label	Clinical trials and/or off-label	5
SMO mutation *c.808G>A, p.(Val270Ile)*	50.58%	Clinical trials and/or off-label	Clinical trials and/or off-label	3
SETD2 deletion *(copy number = 0.84)*		Clinical trials and/or off-label	Clinical trials and/or off-label	4

Sources included in relevant therapies: EMA[1], 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.

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

GNA11 (G protein subunit alpha 11)

Background: The GNA11 gene encodes an alpha subunit of heterotrimeric guanine nucleotide-binding proteins (G-proteins). G-protein alpha subunits bind guanine nucleotide, hydrolyze GTP, and interact with specific receptor and effector molecules. GNA11 is closely related to GNAQ, another G-protein alpha subunit.

Alterations and prevalence: Somatic activating mutations in GNA11 and GNAQ at amino acids R183 and Q209 are common in uveal melanoma and are mutually exclusive. These mutations render the G protein constitutively active leading to the stimulation of MAP kinases, PI3K/AKT, and protein kinase C, which promote tumor growth and proliferation[1,2,3]. Approximately 45% of uveal melanoma cases contain activating mutations in GNA11 and up to 50% of cases contain activating mutations in GNAQ[4,5,6]. By contrast, GNA11 and GNAQ mutations are infrequent in cutaneous melanoma, with a combined prevalence of approximately 1%, and are infrequently observed in other cancers[5,6].

Potential clinical relevance: Currently, no therapies are approved for GNA11 aberrations. In a randomized phase II clinical trial of MEK inhibitor selumetinib versus chemotherapy, GNA11 and GNAQ positive uveal melanoma patients demonstrated a median progression-free survival (PFS) of 15.9 weeks versus 7 weeks, respectively[7]. However, no statistically significant improvement in overall survival (OS) was observed and the improvement in outcomes was associated with a high rate of adverse events[7].

SMO (smoothened, frizzled class receptor)

Background: The SMO gene encodes the smoothened, frizzled class receptor, a transmembrane G protein-coupled receptor that is part of the Hedgehog (Hh) signaling pathway[8]. SMO is negatively regulated by the tumor suppressor gene patched transmembrane receptor (PTCH). However, binding of the ligand sonic hedgehog (Shh) stops this inhibition thereby activating downstream genes such as glioma-associated (GLI) transcription factors[9]. Consequently, aberrations in SMO leading to constitutive activation have been identified to promote oncogenesis in certain cancer types including basal cell carcinoma (BCC)[10,11,12].

Alterations and prevalence: Somatic mutations in SMO are observed in 10% of BCC and medulloblastoma, and in 5% of uterine cancer, 4% of stomach cancer, and 3% of lung adenocarcinoma[5,6]. SMO is amplified in up to 7% of ovarian cancer, 5% of glioma, and 4% of melanoma[5,6].

Potential clinical relevance: Currently, no therapies are approved for SMO aberrations. However, FDA approved Hh pathway inhibitors that include SMO as a target include vismodegib (2012) and sonidegib (2015) for BCC and glasdegib (2018) for acute myeloid leukemia. Several missense mutations in SMO, including G497W and D473Y/H, have been associated with resistance to vismodegib in clinical cohorts of BCC patients[13,14,15]. Similarly, in a clinical trial of BCC patients treated with sonidegib, SMO W535L, Q477E, D473H, S533N, and D473G mutations demonstrated progressive disease[16].

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 Melanoma
GNA11 mutation Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
BAP1 mutation Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
FANCD2 deletion Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
ATR deletion Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
SETD2 mutation Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
SMO 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

GNA11 mutation

Relevant Therapy	EMA	ESMO	NCCN	Clinical Trials*
selumetinib, ulixertinib	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	● (I/II)
cobimetinib	✖	✖	✖	● (I/II)
lifirafenib, mirdametinib	✖	✖	✖	● (I/II)
LXS-196	✖	✖	✖	● (I/II)
abemaciclib, cetuximab, chemotherapy, encorafenib, LY3214996, midazolam	✖	✖	✖	● (I)
everolimus + RO-5126766, RO-5126766	✖	✖	✖	● (I)
LXH254	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	● (I)

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

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

BAP1 mutation

Relevant Therapy	EMA	ESMO	NCCN	Clinical Trials*
atezolizumab	✖	✖	✖	● (II)
durvalumab + olaparib	✖	✖	✖	● (II)
niraparib	✖	✖	✖	● (II)
olaparib	✖	✖	✖	● (II)
BAY-1895344	✖	✖	✖	● (I/II)
pamiparib, tislelizumab	✖	✖	✖	● (I)

FANCD2 deletion

Relevant Therapy	EMA	ESMO	NCCN	Clinical Trials*
durvalumab + olaparib	✖	✖	✖	● (II)
olaparib	✖	✖	✖	● (II)
prexasertib	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	● (II)
BAY-1895344	✖	✖	✖	● (I/II)

ATR deletion

Relevant Therapy	EMA	ESMO	NCCN	Clinical Trials*
durvalumab + olaparib	✖	✖	✖	● (II)
olaparib	✖	✖	✖	● (II)
prexasertib	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	● (II)
BAY-1895344	✖	✖	✖	● (I/II)

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

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

SETD2 mutation

Relevant Therapy	EMA	ESMO	NCCN	Clinical Trials*
atezolizumab	✖	✖	✖	● (II)
olaparib	✖	✖	✖	● (II)
BAY-1895344	✖	✖	✖	● (I/II)
pamiparib, tislelizumab	✖	✖	✖	● (I)

SMO mutation

Relevant Therapy	EMA	ESMO	NCCN	Clinical Trials*
vismodegib	✖	✖	✖	● (II)

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

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 Clinical Trials Information

Clinical Trials information is current as of 2019-09-09. 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'.

GNA11 mutation

NCT03947385
A Phase I/II Study of IDE196 in Patients With Solid Tumors Harboring GNAQ/11 Mutations or PRKC Fusions

Cancer type: Melanoma

Variant class: GNA11 mutation

Other identifier: IDE196-001

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

Exclusion criteria variant class: Microsatellite instability-High

Phase: I/II

Therapy: LXS-196

Locations: Australia, United States

US States: PA, TN, TX

Contact: Dr. Julie Hambleton [650-262-3603; jhambleton@ideayabio.com]

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: Melanoma

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, Italy, United Kingdom, United States

US States: AZ, CA, PA

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

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

GNA11 mutation (continued)

NCT03905148
A Phase Ib, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of a RAF Dimer Inhibitor BGB-283 in Combination With MEK Inhibitor PD-0325901 in Patients With Advanced or Refractory Solid Tumors

Cancer type: Melanoma

Variant class: RAS/RAF/MEK/ERK pathway

Other identifier: BGB-283/PD-0325901-AU-001

Population segments: Locally advanced, Metastatic, Second line, Stage III, Stage IV, Unresectable

Phase: I/II

Therapies: lifirafenib, mirdametinib

Location: Australia

NCT03155620
NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol

Cancer type: Unspecified Solid Tumor

Variant class: RAS/RAF/MEK/ERK mutation

Other identifiers: 17-729, APEC1621SC, COGAPEC1621SC, N 55017 SC, NCI-2017-01251, NCI-COG Pediatric MATCH, Pediatric MATCH

Population segments: Aggressive, Indolent, Pediatric or Adolescent, Second line, Stage III, Stage IV

Phase: II

Therapies: selumetinib, ulixertinib

Locations: Puerto Rico, United States

US States: AL, AR, AZ, CA, CO, CT, DC, DE, FL, GA, HI, IA, ID, IL, IN, KY, LA, MA, MD, ME, MI, MN, MO, MS, NC, NE, NH, NJ, NV, NY, OH, OK, OR, PA, RI, SC, TN, TX, UT, VA, VT, WA, WI

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

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]

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

GNA11 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

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: RAS/RAF/MEK/ERK mutation

Other identifiers: 18-559, 19683, NCI-2018-02064, RMC-4630-01, UCI-18-14

Population segments: KRAS, 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]

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, 2016-0544, EudraCT Number: 2016-001907-21, F18132, I8S-MC-JUAB, I8S-MC-JUAB-c, JapicCTI-194728, JUAB, NCI-2017-00039

Population segments: Adenocarcinoma, BRAF, Fourth line or greater, Large Cell, Stage III, Stage IV

Phase: I

Therapies: abemaciclib, cetuximab, chemotherapy, encorafenib, LY3214996, midazolam

Locations: Australia, France, Japan, United States

US States: DC, FL, MA, NH, PA, TN, TX

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

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

GNA11 mutation (continued)

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, 18-108, 2015-0913, CLXH254X2101, EudraCT Number: 2015-003421-33, JapicCTI-163224, NCI-2015-02280, NL55506.078.15, Nov RAFi (CLXH254X2101), REec-2016-2132, SNCTP000002708

Population segments: BRAF, Fourth line or greater, Second line, Stage I, Stage II, Stage III, Stage IV, Third line

Phase: I

Therapy: LXH254

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

US States: MA, NY, TX

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

BAP1 mutation

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: Melanoma

Variant class: BAP1 mutation

Other identifiers: OCR15732, UF-ETG-001, UF-STO-ETI-001

Population segments: (N/A), Second line

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

Phase: II

Therapy: niraparib

Location: United States

US State: FL

Contact: Project Management Office [352-273-6772; PMO@cancer.ufl.edu]

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

BAP1 mutation (continued)

NCT03925350
A Phase II Study of Niraparib in Patients With Advanced Melanoma With Genetic Homologous Recombination (HR) Mutation / Alteration

Cancer type: Melanoma

Variant class: BAP1 mutation

Other identifier: CPMC17-MEL01

Population segments: Second line, Stage III, Stage IV

Phase: II

Therapy: niraparib

Location: United States

US State: CA

Contact: Peter Gasper [415-600-3472; gasperjp@sutterhealth.org]

No NCT ID - see other identifier(s)
Single Arm, Open label, Signal Seeking, Phase IIa Trial Of The Activity Of Olaparib In Combination With Durvalumab In Patients With Tumours With Homologous Recombination Repair Defects

Cancer type: Unspecified Solid Tumor

Variant class: BAP1 mutation

Other identifiers: ACTRN12617001000392, MoST Addendum 3, U1111-1182-6652

Population segments: Second line, Stage III, Stage IV

Phase: II

Therapy: durvalumab + olaparib

Location: Australia

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: DNA repair 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, United Kingdom

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

BAP1 mutation (continued)

NCT03233204
NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- A Phase II Subprotocol of Olaparib in Patients With Tumors Harboring Defects in DNA Damage Repair Genes

Cancer type: Unspecified Solid Tumor

Variant class: DNA repair pathway

Other identifiers: 20170841, APEC1621H, NCI-2017-00766

Population segments: Aggressive, Indolent, Pediatric or Adolescent, Second line, Stage III, Stage IV

Phase: II

Therapy: olaparib

Locations: Puerto Rico, United States

US States: AL, AR, AZ, CA, CO, DC, FL, GA, IA, ID, IL, IN, KY, LA, MD, ME, MI, MN, MO, MS, NC, NE, NJ, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, VT, WA, WI

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

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: 18-441, 18594, 2017-0186, BAY1895344/18594, EudraCT Number: 2016-004484-39, IRAS ID-218516, JapicCTI-183998, NCI-2018-00206

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

Phase: I/II

Therapy: BAY-1895344

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

US States: FL, GA, MA, NY, OH, PA, TX, UT

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: Fourth line or greater, HER2 negative, Pulmonary, Second line, Stage III, Stage IV, Third line, Triple receptor negative

Phase: I

Therapies: pamiparib, tislelizumab

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

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

Contact: Rob Stewart [clinicaltrials@beigene.com]

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

FANCD2 deletion

No NCT ID - see other identifier(s)
Single Arm, Open label, Signal Seeking, Phase IIa Trial Of The Activity Of Olaparib In Combination With Durvalumab In Patients With Tumours With Homologous Recombination Repair Defects

Cancer type: Unspecified Solid Tumor

Variant class: FANC deletion

Other identifiers: ACTRN12617001000392, MoST Addendum 3, U1111-1182-6652

Population segments: Second line, Stage III, Stage IV

Phase: II

Therapy: durvalumab + olaparib

Location: Australia

NCT03233204
NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- A Phase II Subprotocol of Olaparib in Patients With Tumors Harboring Defects in DNA Damage Repair Genes

Cancer type: Unspecified Solid Tumor

Variant class: DNA repair pathway

Other identifiers: 20170841, APEC1621H, NCI-2017-00766

Population segments: Aggressive, Indolent, Pediatric or Adolescent, Second line, Stage III, Stage IV

Phase: II

Therapy: olaparib

Locations: Puerto Rico, United States

US States: AL, AR, AZ, CA, CO, DC, FL, GA, IA, ID, IL, IN, KY, LA, MD, ME, MI, MN, MO, MS, NC, NE, NJ, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, VT, WA, WI

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

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]

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

FANCD2 deletion (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: 18-441, 18594, 2017-0186, BAY1895344/18594, EudraCT Number: 2016-004484-39, IRAS ID-218516, JapicCTI-183998, NCI-2018-00206

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

Phase: I/II

Therapy: BAY-1895344

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

US States: FL, GA, MA, NY, OH, PA, TX, UT

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

ATR deletion

No NCT ID - see other identifier(s)
Single Arm, Open label, Signal Seeking, Phase IIa Trial Of The Activity Of Olaparib In Combination With Durvalumab In Patients With Tumours With Homologous Recombination Repair Defects

Cancer type: Unspecified Solid Tumor

Variant class: ATR deletion

Other identifiers: ACTRN12617001000392, MoST Addendum 3, U1111-1182-6652

Population segments: Second line, Stage III, Stage IV

Phase: II

Therapy: durvalumab + olaparib

Location: Australia

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

ATR deletion (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: ATR deletion

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]

NCT03233204
NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- A Phase II Subprotocol of Olaparib in Patients With Tumors Harboring Defects in DNA Damage Repair Genes

Cancer type: Unspecified Solid Tumor

Variant class: DNA repair pathway

Other identifiers: 20170841, APEC1621H, NCI-2017-00766

Population segments: Aggressive, Indolent, Pediatric or Adolescent, Second line, Stage III, Stage IV

Phase: II

Therapy: olaparib

Locations: Puerto Rico, United States

US States: AL, AR, AZ, CA, CO, DC, FL, GA, IA, ID, IL, IN, KY, LA, MD, ME, MI, MN, MO, MS, NC, NE, NJ, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, VT, WA, WI

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

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]

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

ATR deletion (continued)

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: 18-441, 18594, 2017-0186, BAY1895344/18594, EudraCT Number: 2016-004484-39, IRAS ID-218516, JapicCTI-183998, NCI-2018-00206

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

Phase: I/II

Therapy: BAY-1895344

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

US States: FL, GA, MA, NY, OH, PA, TX, UT

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

SETD2 mutation

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: DNA repair 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, United Kingdom

NCT03233204
NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- A Phase II Subprotocol of Olaparib in Patients With Tumors Harboring Defects in DNA Damage Repair Genes

Cancer type: Unspecified Solid Tumor

Variant class: DNA repair pathway

Other identifiers: 20170841, APEC1621H, NCI-2017-00766

Population segments: Aggressive, Indolent, Pediatric or Adolescent, Second line, Stage III, Stage IV

Phase: II

Therapy: olaparib

Locations: Puerto Rico, United States

US States: AL, AR, AZ, CA, CO, DC, FL, GA, IA, ID, IL, IN, KY, LA, MD, ME, MI, MN, MO, MS, NC, NE, NJ, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, VT, WA, WI

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

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

SETD2 mutation (continued)

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: 18-441, 18594, 2017-0186, BAY1895344/18594, EudraCT Number: 2016-004484-39, IRAS ID-218516, JapicCTI-183998, NCI-2018-00206

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

Phase: I/II

Therapy: BAY-1895344

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

US States: FL, GA, MA, NY, OH, PA, TX, UT

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: Fourth line or greater, HER2 negative, Pulmonary, Second line, Stage III, Stage IV, Third line, Triple receptor negative

Phase: I

Therapies: pamiparib, tislelizumab

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

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

Contact: Rob Stewart [clinicaltrials@beigene.com]

SMO mutation

No NCT ID - see other identifier(s)
Single Arm, Open Label, Signal Seeking, Phase IIa Trial of The Activity of Vismodegib in Patients With Tumours Harbouring PTCH1 or SMO Mutations

Cancer type: Unspecified Solid Tumor

Variant class: SMO mutation

Other identifiers: ACTRN12618000281291, CTC0141-addendum 4, MoST Addendum 4, U1111-1182-6652

Population segments: Second line, Stage III, Stage IV

Exclusion criteria variant classes: SMO D473Y mutation, SMO G497W mutation, SUFU mutation

Phase: II

Therapy: vismodegib

Locations: Australia, New Zealand

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

SMO mutation (continued)

NCT02465060
Molecular Analysis for Therapy Choice (MATCH)

Cancer type: Unspecified Solid Tumor

Variant class: SMO mutation

Other identifiers: 15-7002, 16-750, AAAP9159, CTSU/EAY131, EAY131, EAY131- K1, EAY131- K2, EAY131- Z1K, EAY131-A, EAY131-B, EAY131-C1, EAY131-C2, EAY131-E, EAY131-F, EAY131-G, EAY131-H, EAY131-I, EAY131-J, EAY131-L, EAY131-M, EAY131-MATCH, EAY131-N, EAY131-P, EAY131-Q, EAY131-R, EAY131-S1, EAY131-S2, EAY131-T, EAY131-U, EAY131-V, EAY131-W, EAY131-X, EAY131-Y, EAY131-Z1A, EAY131-Z1B, EAY131-Z1C, EAY131-Z1D, EAY131-Z1E, EAY131-Z1F, EAY131-Z1G, EAY131-Z1H, EAY131-Z1I, EAY131-Z1J, EAY131-Z1L, EAY131-Z1M, ECOG-ACRIN EAY131, ECOGEAY131-M, MATCH, NCI-2015-00054, NCI-MATCH

Population segments: Aggressive, BRAF, Classical, Fourth line or greater, HER2 positive, Indolent, Nodular lymphocyte-predominant, Pulmonary, Second line, Stage III, Stage IV, Third line, Unspecified

Phase: II

Therapy: vismodegib

Locations: Puerto Rico, United States

US States: AK, AL, AR, AZ, CA, CO, CT, DC, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, ME, MI, MN, MO, MS, MT, NC, ND, NE, NH, NJ, NM, NV, NY, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY

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

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

Cancer type: Unspecified Solid Tumor

Variant class: SMO 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: vismodegib

Location: Canada

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.

GNA11 mutation

Variant Class	Evidence Items
RAS/RAF/MEK/ERK pathway	5
↳ RAS/RAF/MEK/ERK mutation	3
↳ GNA11 mutation	1

BAP1 mutation

Variant Class	Evidence Items
DNA repair pathway	8
↳ DNA repair mutation	4
↳ BAP1 mutation	3

FANCD2 deletion

Variant Class	Evidence Items
DNA repair pathway	8
↳ DNA repair deletion	0
↳ FANCD2 deletion	0
Fanconi anemia pathway	3
↳ FANC deletion	1
↳ FANCD2 deletion	0

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.

ATR deletion

Variant Class	Evidence Items
DNA repair pathway	8
↳ DNA repair deletion	0
↳ ATR deletion	2
Fanconi anemia pathway	3
↳ ATR deletion	2

SETD2 mutation

Variant Class	Evidence Items
DNA repair pathway	8
↳ DNA repair mutation	4
↳ SETD2 mutation	0

SMO mutation

Variant Class	Evidence Items
SMO aberration	1
↳ SMO mutation	2

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. Luke et al. Biology of advanced uveal melanoma and next steps for clinical therapeutics. Pigment Cell Melanoma Res. 2015 Mar;28(2):135-47. PMID: 25113308
2. Amaro et al. The biology of uveal melanoma. Cancer Metastasis Rev. 2017 Mar;36(1):109-140. PMID: 28229253
3. Parish et al. GNAS, GNAQ, and GNA11 alterations in patients with diverse cancers. Cancer. 2018 Oct 15;124(20):4080-4089. PMID: 30204251
4. Van et al. Mutations in GNA11 in uveal melanoma. N. Engl. J. Med. 2010 Dec 2;363(23):2191-9. PMID: 21083380
5. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
6. 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
7. Carvajal et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. JAMA. 2014 Jun 18;311(23):2397-405. PMID: 24938562
8. Athar et al. Hedgehog signalling in skin development and cancer. Exp. Dermatol. 2006 Sep;15(9):667-77. PMID: 16881963
9. Rimkus et al. Targeting the Sonic Hedgehog Signaling Pathway: Review of Smoothened and GLI Inhibitors. Cancers (Basel). 2016 Feb 15;8(2). PMID: 26891329
10. Scales et al. Mechanisms of Hedgehog pathway activation in cancer and implications for therapy. Trends Pharmacol. Sci. 2009 Jun;30(6):303-12. PMID: 19443052
11. Gonnissen et al. Targeting the Hedgehog signaling pathway in cancer: beyond Smoothened. Oncotarget. 2015 Jun 10;6(16):13899-913. PMID: 26053182
12. Rubin et al. Targeting the Hedgehog pathway in cancer. Nat Rev Drug Discov. 2006 Dec;5(12):1026-33. PMID: 17139287
13. Pricl et al. Smoothened (SMO) receptor mutations dictate resistance to vismodegib in basal cell carcinoma. Mol Oncol. 2015 Feb;9(2):389-97. doi: 10.1016/j.molonc.2014.09.003. Epub 2014 Sep 26. PMID: 25306392
14. Dijkgraaf et al. Small molecule inhibition of GDC-0449 refractory smoothened mutants and downstream mechanisms of drug resistance. Cancer Res. 2011 Jan 15;71(2):435-44. PMID: 21123452
15. Yauch et al. Smoothened mutation confers resistance to a Hedgehog pathway inhibitor in medulloblastoma. Science. 2009 Oct 23;326(5952):572-4. PMID: 19726788
16. Danial et al. An Investigator-Initiated Open-Label Trial of Sonidegib in Advanced Basal Cell Carcinoma Patients Resistant to Vismodegib. Clin. Cancer Res. 2016 Mar 15;22(6):1325-9. PMID: 26546616

Report Authorised by

Signed

printed

Keeda Hardisty

Clinical Scientist [X]

Pathologist [ ]

Report reviewed by

Signed

printed

Kaiya Chowdhary

Clinical Scientist [X]

BMS [ ]

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