



[Oncofocus] Patient Test Report

Surname

Requesting clinician

Forename

DOB

Date requested

Gender

24/01/2017

Histology #

Tumour %

Primary site Unknown

Tumour % 80

Tumour subtype Liver And Neuroendocrine CUP

(macrodissected)

Tissue type Liver

Comment:

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

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

The following actionable variants were detected:

Variant Summary

Sample Cancer Type: Unknown Primary Origin

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

Gene Variant	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials
TSC2 p.(I1797fs) c.5388delC	✗	✗	✗	✗	📍 (12)

EMA: European Medicine Agency, **US-FDA:** United States-Food and Drug Administration, **ESMO:** European Society for Medical Oncology, **US-NCCN:** United States-National Comprehensive Cancer Network. Numbers in parentheses indicate the number of relevant therapies with evidence. Hotspot variants with >10% alternate allele reads, and in >10 unique reads are classified as 'detected' with an assay sensitivity and positive predictive value of 92%. Copy number variants; amplifications of a >5% confidence value of ≥4 after normalization and deletions of ≤1 are classified as present when the tumour% >50%. Gene Fusions are reported when occurring in >20 counts and meeting the thresholds of assay specific internal RNA quality control. With a sensitivity of 92% and PPV of 99%. Supplementary technical information is available upon request.

ONC17-: 0016

www.oncologica.com

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

Relevant Therapy Summary

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

TSC2 p.(I1797fs) c.5388_5388delC

Relevant Therapy	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials*
AZD-5363 + olaparib	×	×	×	×	🕒 (I)
everolimus	×	×	×	×	● (II)
olaparib + vistusertib	×	×	×	×	● (II)
temsirolimus	×	×	×	×	● (II)
MSC-2363318A	×	×	×	×	● (I)
palbociclib + pictilisib, palbociclib + taselisib	×	×	×	×	● (I)
PQR-309	×	×	×	×	● (I)
gedatolisib	×	×	×	×	○ (II)
LY-3023414	×	×	×	×	○ (II)
sirolimus	×	×	×	×	○ (II)
selumetinib + vistusertib	×	×	×	×	○ (I/II)
LY-3023414, LY-3023414 + midazolam	×	×	×	×	○ (I)

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

Current Global Clinical Trials Information

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

TSC2 p.(I1797fs) c.5388_5388delC

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: TSC2 mutation

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

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

Phase: II

Therapy: everolimus

Country: France

NCT02201212

A Phase II Trial of Everolimus for Cancer Patients With Inactivating Mutations in TSC1 or TSC2

Cancer type: Unspecified Cancer

Variant class: TSC2 mutation

Other identifiers: 14-229, CRAD001MUS217T, NCI-2015-00624, TrialTroveID-213682

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

Phase: II

Therapy: everolimus

Country: United States

US States: MA, NY

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

TSC2 p.(I1797fs) c.5388_5388delC (continued)**NCT02352844**

Phase II Study of Everolimus in Patients With Advanced Solid Malignancies With TSC1 and TSC2 Mutations

Cancer type: Unspecified Solid Tumor**Variant class:** TSC2 mutation**Other identifiers:** 15-x018, TrialTroveID-251524**Population segments:** First line, Second line or greater/Refractory/Relapsed, Stage III, Stage IV**Phase:** II**Therapy:** everolimus**Country:** United States**US State:** MO**US Contact:** Dr. Saiama Waqar [314-362-5737; swaqar@dom.wustl.edu]**NCT02576444**

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

Cancer type: Unspecified Solid Tumor**Variant class:** TSC2 mutation**Other identifiers:** 1508016363, OLAPCO, TrialTroveID-266161**Population segments:** First line, Second line or greater/Refractory/Relapsed, Stage IV**Phase:** II**Therapy:** olaparib + vistusertib**Country:** United States**US State:** CT**US Contact:** Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.**NCT02693535**

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

Cancer type: Unspecified Solid Tumor**Variant class:** TSC mutation**Other identifiers:** Pro00014171, TAPUR, TrialTroveID-273941**Population segments:** (N/A), Aggressive, Diffuse large B-cell lymphoma (DLBCL), Second line or greater/Refractory/Relapsed, Stage III, Stage IV**Phase:** II**Therapy:** temsirolimus**Country:** United States**US States:** MI, NC**US Contact:** Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

TSC2 p.(I1797fs) c.5388_5388delC (continued)**NCT01971515**

A Phase I, First-in-Human, Dose Escalation Trial of MSC2363318A, a Dual p70S6K/Akt Inhibitor, in Subjects With Advanced Malignancies

Cancer type: Unspecified Solid Tumor

Variant class: TSC2 aberration

Other identifiers: 2013-0525, CHRMS 14-081, EMR100018-001, NCI-2013-02370, TrialTroveID-196334

Population segments: Aggressive, Classical, EGFR, HER2 positive, Indolent, Nodular lymphocyte-predominant, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapy: MSC-2363318A

Country: United States

US States: CA, MI, TX, VT

US Contact: US Medical Information [888-275-7376]

NCT02338622

A Phase I Multi-centre Trial of the Combination of Olaparib (PARP Inhibitor) and AZD5363 (AKT Inhibitor) in Patients With Advanced Solid Tumours

Cancer type: Unspecified Solid Tumor

Variant class: PI3K/AKT/MTOR pathway

Other identifiers: 14/LO/0103, CCR4058, ComPAKT, CRUKD/14/004, EudraCT number: 2013-004692-13, TrialTroveID-213474, UKCRN ID 16550

Population segments: HER2 negative, Hormone refractory, Second line or greater/Refractory/Relapsed, Stage III, Stage IV, Triple receptor negative

Phase: I

Therapy: AZD-5363 + olaparib

Country: United Kingdom

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, TrialTroveID-253778

Population segments: HER2 negative, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I

Therapies: palbociclib + pictilisib, palbociclib + tasisib

Country: United Kingdom

TSC2 p.(I1797fs) c.5388_5388delC (continued)**NCT02483858**

Phase I Study of Oral PQR309 in Patients With Advanced Solid Tumors.

Cancer type: Unspecified Solid Tumor**Variant class:** PI3K/AKT/MTOR pathway**Other identifiers:** EudraCT Number: 2015-003919-38, I 258914, IRAS ID: 193390, PQR309-003, REec-2016-2264, TrialTroveID-260655**Population segments:** Second line or greater/Refractory/Relapsed, Stage III, Stage IV**Phase:** I**Therapy:** PQR-309**Country:** United States**US State:** NY**US Contact:** Dr. Alex Adjei [Alex.Adjei@RoswellPark.org]**No NCT ID - see other identifier(s)**

Phase II Study of Gedatolisib in Advanced Recurrent Small-Cell Lung Cancer Patients Harboring Molecular Alterations in PI3K/AKT/mTOR Pathway (EAGLE-PAT)

Cancer type: Small Cell Lung Cancer**Variant class:** TSC2 aberration**Other identifiers:** EAGLE-PAT, TrialTroveID-268816, UMIN000020585**Population segments:** Extensive, Second line or greater/Refractory/Relapsed**Exclusion criteria variant classes:** BRAF V600E mutation (Small Cell Lung Cancer), KRAS activating mutation (Small Cell Lung Cancer)**Phase:** II**Therapy:** gedatolisib**Country:** Japan**NCT02646319**

A Pilot Study of a Rapid Access Platform for Investigational Drugs (RAPID) in Advanced Cancers

Cancer type: Bladder Cancer, Breast Cancer, Endometrial Cancer, Head and Neck Cancer, Kidney Cancer, Ovarian Cancer, Soft Tissue Sarcoma**Variant class:** TSC2 aberration**Other identifiers:** MC1313, NCI-2015-02151, RAPID, TrialTroveID-270911**Population segments:** Second line or greater/Refractory/Relapsed, Stage III, Stage IV**Phase:** II**Therapy:** sirolimus**Country:** United States**US States:** AZ, MN**US Contact:** Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

TSC2 p.(I1797fs) c.5388_5388delC (continued)**NCT02549989**

Single-Arm, Open-Label, Phase II Study of LY3023414 for the Treatment of Recurrent or Persistent Endometrial Cancer

Cancer type: Endometrial Cancer

Variant class: PI3K/AKT/MTOR pathway

Other identifiers: 15-079, TrialTroveID-264675

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

Exclusion criteria variant class: RAS/RAF/MEK/ERK pathway (Endometrial Cancer)

Phase: II

Therapy: LY-3023414

Country: United States

US States: NJ, NY

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

NCT02583542

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

Cancer type: Breast Cancer, Colorectal Cancer, Endometrial Cancer, Kidney Cancer, Melanoma, Non-Small Cell Lung Cancer, Ovarian Cancer, Pancreatic Cancer, Thyroid Cancer

Variant class: PI3K/AKT/MTOR pathway

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

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

Phase: I/II

Therapy: selumetinib + vistusertib

Country: United Kingdom

NCT02338622

A Phase I Multi-centre Trial of the Combination of Olaparib (PARP Inhibitor) and AZD5363 (AKT Inhibitor) in Patients With Advanced Solid Tumours

Cancer type: Breast Cancer

Variant class: PI3K/AKT/MTOR pathway

Other identifiers: 14/LO/0103, CCR4058, ComPAKT, CRUKD/14/004, EudraCT number: 2013-004692-13, TrialTroveID-213474, UKCRN ID 16550

Population segments: HER2 negative, Hormone refractory, Second line or greater/Refractory/Relapsed, Stage III, Stage IV, Triple receptor negative

Other inclusion criteria: ERBB2 wild type, ER negative, PR negative

Phase: I

Therapy: AZD-5363 + olaparib

Country: United Kingdom

TSC2 p.(I1797fs) c.5388_5388delC (continued)**NCT01655225**

A Phase I First-in-Human Dose Study of LY3023414 in Patients With Advanced Cancer

Cancer type: Non-Small Cell Lung Cancer

Variant class: PI3K/AKT/MTOR pathway

Other identifiers: 12-286, 13517, I6A-MC-CBBA, REFMAL 276, TrialTroveID-172222

Population segments: Extranodal marginal zone B-cell lymphoma (MALT), First line, Follicular lymphoma (FL), HER2 negative, Indolent, Other subtype, Second line or greater/Refractory/Relapsed, Small lymphocytic lymphoma (SLL), Squamous Cell, Stage III, Stage IV, Untreated, Waldenstrom`s macroglobulinemia (WM)

Phase: I

Therapies: LY-3023414, LY-3023414 + midazolam

Countries: Italy, United States

US States: NY, OK, PA, TN

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

Appendix: Evidence Summary by Variant Class

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

TSC2 p.(I1797fs) c.5388_5388delC

Variant Class	Evidence Items
PI3K/AKT/MTOR pathway	7
↳ TSC2 aberration	3
↳ TSC2 mutation	4
↳ TSC mutation	1
↳ TSC2 mutation	4

Appendix: Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency Transcript	Variant Effect
TSC2	p.(I1797fs)	c.5388_5388delC	.	chr16:2138574	26.71% NM_000548.3	frameshift Deletion

TERMS AND CONDITIONS

The following paragraph on Liability is an extract from the Oncologica Tests' Terms and Conditions. The extract is to draw your attention to particular terms applicable to you but nothing set out here is intended to supersede or override our Terms and Conditions, which can be found on our website at www.oncologica.com under the title Oncologica Tests' Terms and Conditions. Please read these Oncologica Test Terms and Conditions carefully before you submit an order for the Oncologica Tests, as you will be bound by these Terms and Conditions, once a contract comes into existence as per paragraph 2 of the Oncologica Test's Terms and Conditions.

6. Liability

6.1 Oncologica operates in compliance with international ISO15189:2012 standards and is regulated by UKAS. The Oncologica Tests have not been cleared or approved by the United States Food and Drug Administration; however, such clearance or approval is not required.

6.2 The Patient agrees that the Oncologica Test Report is intended for clinical use and interpretation by a physician who is experienced and skilled in the use and interpretation of clinical test data. The Oncologica Test Report is based on the Sample submitted by the Patient. The Oncologica Test Report should not be considered or its contents applied to any other patient or any other sample. Oncologica does not update an Oncologica Test Report once it has been sent.

6.3 Information compiled in the Oncologica Test Report includes is from publicly available as well as proprietary sources. By updating the source database, Oncologica makes every effort to provide the most accurate and up-to-date information. However, Oncologica does not warrant or represent that the information in the Oncologica Test Report is accurate, timely or complete.

6.4 The Oncologica Test Report contains drug and clinical trial information. However, Oncologica does not warrant or represent that any drug or clinical trial identified by the Oncologica Test will guarantee a therapeutic response for a particular Patient. The drugs listed in an Oncologica Test Report are ranked on clinical evidence as to the predicted efficacy or appropriateness for the Patient. The Patient shall ensure that its physician shall evaluate and interpret the Oncologica Test Report, along with all other available clinical information about the Patient, to determine the best treatment decisions in their own independent medical judgment. Patient management decisions should not be based on a single test, nor solely on the information contained in the Oncologica Test Report.

6.5 Subject to paragraph **6.10**, Oncologica shall have no liability for any use made of the information provided in the Oncologica Test Report, including but not limited to any report prepared by Oncologica summarising the results of the Oncologica Tests, any advice supplied by Oncologica, any decisions taken, or for any costs incurred by Patient and/or the Patient's physician and/or the Agent in consequence of such use, advice or decisions. The Oncologica Test and/or the Oncologica Test Report is not a substitute for the Patient's physician's professional judgment. The use of the information provided in the Oncologica Test Report is provided as a tool for the ordering physician's use in determining the appropriate treatment for the Patient. The decision as to what course of treatment and the appropriate use of the information provided by the Oncologica Test Report is solely that of the Patient's physician.

6.6 Oncologica does not warrant or represent or guarantee that the Oncologica Tests will identify an actionable genetic alteration that is linked to anti-cancer targeted therapies. Although the Oncologica Tests are comprehensive, in a proportion of Patients, the Oncologica Test result may not identify any actionable mutations for a patient's cancer. In the event that no actionable alteration in the Sample is identified by the Oncologica Test, then the Patient is still under full obligation to pay the Charges and no refund is available to the Patient and/or Agent.

6.7 The Oncologica Test identifies genomic actionable alterations found in the submitted Sample that are linked to anti-cancer targeted agents. Also note that this test only examines tumour, and not normal tissue from the patient, and therefore cannot distinguish between somatic and germline (i.e., heritable) alterations.

6.8 Subject to Clause **6.8**, Oncologica shall not be liable to the Patient whether in contract, tort (including negligence and breach of statutory duty), or otherwise for any:

(a) Error or defect in the Oncologica Test Report as a result of any inaccurate or incomplete information supplied by the Patient;

(b) Loss of data or materials, including the Sample and/or the Report and including any loss arising as a result of the acts or omissions of a courier;

(c) Indirect or consequential loss arising whether or not advised of the possibility of the same.

6.9 Subject to the provisions of this Clause 6, Oncologica's total liability to the Patient in respect of all losses arising under or in connection with the Contract, whether in contract, tort (including negligence and breach of statutory duty), or otherwise, shall in no circumstances exceed the Charges paid for the Test that is the subject of the claim.

6.10 Nothing in the Contract limits or excludes the liability of Oncologica for breach of its obligations under section 12 of the Sale of Goods Act 1979 and/or section 2 of the Supply of Goods and Services Act 1982; death or personal injury resulting from negligence; or fraud or fraudulent misrepresentation.

6.11 If the Patient is a consumer (and not a business), the Patient expressly acknowledges and agrees that the Test is supplied to the Patient's specification and therefore there is no right to cancel the Test following acceptance under Clause 2.2. If the Patient is a consumer, then notwithstanding any other provisions of the Contract, none of the Patient's consumer statutory rights are affected.

