[Oncofocus] Patient Test Report

Oncologica UK Ltd
Suite 15-16, The Science Village
Chesterford Research Park
Cambridge, CB10 1XL, UK
Tel: +44(0)1223 785327
Email: info@oncologica.com

Histology #		**Tumour %**	70
Primary site	Ovary	**Tumour % (macrodissected)**	
Tumour subtype	Serous Adenocarcinoma		
Tissue type	Ovary		

Comment: This is a final report which replaces the interim report (dated 14/12/16) and reflects the results from additional testing.
The DNA and RNA extracted from this sample were of optimal quality. The Oncofocus assay on which the sample was run met all assay specific quality metrics.

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

The following actionable variants were detected:

Notably the TP53 and BRCA1 aberrations was detected are at a high allele frequency raising the possibility that these are germline mutations. However, the Oncofocus test is unable to distinguish somatic from germline mutations.

Variant Summary

Sample Cancer Type: Ovarian Cancer

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

Gene Variant	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials
BRCA1 p.(A1714fs) c.5139_5140insAT	● (1)	✖	✖	✖	● (5)
TP53 p.(R196Ter) c.586C>T	✖	✖	✖	✖	● (9)
MYC amplification	✖	✖	✖	✖	● (1)

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

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.

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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

BRCA1 p.(A1714fs) c.5139_5140insAT

Relevant Therapy	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials*
olaparib	●	✖	✖	✖	● (IV)
niraparib	✖	✖	✖	✖	● (III)
bevacizumab, bevacizumab + niraparib, niraparib	✖	✖	✖	✖	● (I/II)
olaparib + chemotherapy	✖	✖	✖	✖	● (I/II)
talazoparib + chemotherapy	✖	✖	✖	✖	● (I)

TP53 p.(R196Ter) c.586C>T

Relevant Therapy	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials*
MK-1775 + chemotherapy	✖	✖	✖	✖	● (II)
MK-1775 + olaparib	✖	✖	✖	✖	● (II)
APR-246 + chemotherapy	✖	✖	✖	✖	● (I/II)
ganetespib + chemotherapy	✖	✖	✖	✖	● (I/II)
chemotherapy + p53MVA	✖	✖	✖	✖	● (I)
COTI-2	✖	✖	✖	✖	● (I)
ixazomib + vorinostat	✖	✖	✖	✖	● (I)
MK-1775	✖	✖	✖	✖	● (I)
SGT-53, SGT-53 + chemotherapy	✖	✖	✖	✖	● (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.

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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

MYC amplification

Relevant Therapy	EMA	US-FDA	ESMO	US-NCCN	Global Clinical Trials*
INCB-54329	✖	✖	✖	✖	● (I/II)

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

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Current EMA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated

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

BRCA1 p.(A1714fs) c.5139_5140insAT

● olaparib

Cancer type: Ovarian Cancer **Label as of:** 2016-04-13 **Variant class:** BRCA mutation

Reference:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003726/WC500180151.pdf

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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'.

BRCA1 p.(A1714fs) c.5139_5140insAT

NCT02476968
An Open Label, Single Arm, Multicentre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed Somatic or Germline BRCA Mutated Ovarian Cancer Patients Who Are in Complete or Partial Response Following Platinum Based Chemotherapy (ORZORA).

Cancer type: Ovarian Cancer

Variant class: BRCA1 mutation

Other identifiers: D0816C00012, EudraCT Number: 2015-000734-30, IRAS ID: 177196, ORZORA, REec-2015-1634, TrialTroveID-260119

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

Phase: IV

Therapy: olaparib

Countries: Bulgaria, Canada, Czech Republic, Hungary, Italy, Poland, Spain, United Kingdom

NCT02503436
C-PATROL - A Single Arm, Prospective Non-interventional Study (NIS) to Collect Clinical and Patient Reported Outcome Data in an Olaparib Treated BRCAm+ PSR Ovarian Cancer Population

Cancer type: Ovarian Cancer

Variant class: BRCA1 mutation

Other identifiers: C-PATROL, D0816R00009, TrialTroveID-261874

Population segments: (N/A), Maintenance/Consolidation

Phase: IV

Therapy: olaparib

Country: Germany

NCT02655016
A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients With HRD-Positive Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy

Cancer type: Ovarian Cancer

Variant class: BRCA mutation

Other identifiers: ENGOT-ov 26, EudraCT Number: 2015-000952-11, NCI-2016-00574, PR-30-5017-C, PRIMA, TrialTroveID-252552

Population segments: Maintenance/Consolidation, Stage III, Stage IV

Phase: III

Therapy: niraparib

Country: United States

US States: CA, LA, MA, MD, NY, OH, OK, OR, PA, SD, WA

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

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BRCA1 p.(A1714fs) c.5139_5140insAT (continued)

NCT02684318
Phase Ib/II Study to Evaluate the Efficacy and Tolerability of PM01183 in Combination With Olaparib in Patients With Advanced Solid Tumors

Cancer type: Ovarian Cancer

Variant class: BRCA1 mutation

Other identifiers: EudraCT Number: 2015-001141-80, POLA, POLA/ACOG1401, TrialTroveID-263173

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

Phase: I/II

Therapy: olaparib + chemotherapy

Country: Spain

NCT02354131
AVANOVA1 - Phase I of Bevacizumab-Niraparib Combination. AVANOVA2 -A 3-arm, Phase II Randomized Study of Niraparib &/or Niraparib-bevacizumab Combination Against Bevacizumab Alone in HRD Platinum-sensitive Epithelial Ovarian Cancer.

Cancer type: Ovarian Cancer

Variant class: BRCA mutation

Other identifiers: AVANOVA, AVANOVA1, AVANOVA2, ENGOT-ov24 - AVANOVA: NSGO, ENGOT-OV24-NSGO/AVANOVA, EudraCT Number: 2014-004269-26, TrialTroveID-251559

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

Phase: I/II

Therapies: bevacizumab, bevacizumab + niraparib, niraparib

Country: Denmark

NCT02693535
Targeted Agent and Profiling Utilization Registry (TAPUR) Study

Cancer type: Unspecified Solid Tumor

Variant class: BRCA1 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: olaparib

Country: United States

US States: MI, NC

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

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BRCA1 p.(A1714fs) c.5139_5140insAT (continued)

NCT02317874
A Phase I Study of BMN 673 in Combination with Carboplatin and Paclitaxel in Patients with Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: BRCA1 mutation

Other identifiers: 051513, 9782, NCI 9782, NCI-2014-02474, TrialTroveID-248774

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

Phase: I

Therapy: talazoparib + chemotherapy

Country: United States

US States: NJ, WI

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

TP53 p.(R196Ter) c.586C>T

NCT02272790
A Multicentre Phase II Study of AZD1775 Plus Chemotherapy in Patients With Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Cancer type: Ovarian Cancer

Variant class: TP53 mutation

Other identifiers: 14-268, 14-547, 15401, 18114, AAAO8156, D6010C00004, EudraCT Number: 2015-000886-30, IRAS ID: 168445, TrialTroveID-219301

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

Phase: II

Therapy: MK-1775 + chemotherapy

Countries: Canada, United Kingdom, United States

US States: AZ, CA, FL, GA, MA, NY, OH, OK, OR, PA, TN, TX, WI

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

NCT02098343
PiSARRO: p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin Combination Chemotherapy With or Without APR-246

Cancer type: Ovarian Cancer

Variant class: TP53 mutation

Other identifiers: APR-246-02, APR-407, EudraCT Number: 2013-001472-38, EUTROC PiSARRO, IRAS 137274, PiSARRO, REec-2016-2092, TrialTroveID-128680

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

Phase: I/II

Therapy: APR-246 + chemotherapy

Countries: Belgium, Netherlands, Spain, United Kingdom

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TP53 p.(R196Ter) c.586C>T (continued)

NCT02012192
A Two-part, Multicentre, International Phase I and II Trial Assessing the Safety and Efficacy of the Hsp90 Inhibitor Ganetespib in Combination With Paclitaxel Weekly in Women With High-grade Serous, High-grade Endometrioid, or Undifferentiated, Platinum-resistant Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer Ganetespib in metastatic, p53 mutant, platinum-resistant ovarian cancer (GANNET53)

Cancer type: Ovarian Cancer

Variant class: TP53 mutation

Other identifiers: DRKS00005501, EudraCT Number: 2013-003868-31, GANNET53, TrialTroveID-199233

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

Phase: I/II

Therapy: ganetespib + chemotherapy

Countries: Austria, Belgium, France, Germany

NCT02275039
A Phase I Study of a p53MVA Vaccine in Combination With Gemcitabine in Ovarian Cancer

Cancer type: Ovarian Cancer

Variant class: TP53 mutation

Other identifiers: 13373, NCI-2014-02169, TrialTroveID-219643

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

Phase: I

Therapy: chemotherapy + p53MVA

Country: United States

US State: CA

US Contact: Mihaela C. Cristea [800-826-4673; becomingapatient@coh.org]

NCT02433626
A Phase 1b Study of Coti-2 for the Treatment of Advanced or Recurrent Gynecologic Malignancies

Cancer type: Ovarian Cancer

Variant class: TP53 mutation

Other identifiers: 2015-0035, COTI2-101, DRUG COTI2-101, NCI-2015-01738, TrialTroveID-198183

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

Phase: I

Therapy: COTI-2

Country: United States

US States: IL, TX

US Contact: Ashley ten Haaf [519-858-5157; atenhaaf@criticaloutcome.com]

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TP53 p.(R196Ter) c.586C>T (continued)

NCT02576444
A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: TP53 mutation

Other identifiers: 1508016363, OLAPCO, TrialTroveID-266161

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

Phase: II

Therapy: MK-1775 + olaparib

Country: United States

US State: CT

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

NCT02042989
A Phase I Study of MLN9708 and Vorinostat to Target Autophagy in Patients With Advanced p53 Mutant Malignancies

Cancer type: Unspecified Solid Tumor

Variant class: TP53 mutation

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

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

Phase: I

Therapy: ixazomib + vorinostat

Country: United States

US State: TX

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

NCT02610075
A Phase Ib Study to Determine the Maximum Tolerated Dose (MTD) of AZD1775 Monotherapy in Patients With Locally Advanced or Metastatic Solid Tumours.

Cancer type: Unspecified Solid Tumor

Variant class: TP53 mutation

Other identifiers: D6015C00003, REFMAL 398, TrialTroveID- 268385

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

Phase: I

Therapy: MK-1775

Country: United States

US States: CO, TN

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

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TP53 p.(R196Ter) c.586C>T (continued)

NCT02354547
A Phase I Study of SGT-53, a TfRscFv-Liposome-p53 Complex, in Children with Refractory or Recurrent Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: TP53 mutation

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

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

Phase: I

Therapies: SGT-53, SGT-53 + chemotherapy

Country: United States

US State: TX

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

MYC amplification

NCT02431260
A Phase I, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB054329 in Subjects With Advanced Malignancies

Cancer type: Unspecified Solid Tumor

Variant class: MYC aberration

Other identifiers: 2015-0054, INCB 54329-101, NCI-2015-00936, TrialTroveID-252118, UMCC 2015.032, UW15024

Population segments: Aggressive, Classical, Diffuse large B-cell lymphoma (DLBCL), Hormone refractory, Indolent, Nodular lymphocyte-predominant, Other subtype, Second line or greater/Refractory/Relapsed, Stage III, Stage IV

Phase: I/II

Therapy: INCB-54329

Country: United States

US States: CA, CO, IL, IN, MI, MO, TN, TX, WA

US Contact: Incyte Corporation Call Center [855-463-3463]

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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.

BRCA1 p.(A1714fs) c.5139_5140insAT

Variant Class	Evidence Items
BRCA mutation	3
↳ BRCA1 mutation	5

TP53 p.(R196Ter) c.586C>T

Variant Class	Evidence Items
TP53 mutation	9

MYC amplification

Variant Class	Evidence Items
MYC aberration	1
↳ MYC amplification	0

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Appendix: Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRCA1	p.(A1714fs)	c.5139_5140insAT	.	chr17:41215966	65.29%	NM_007300.3	frameshift Insertion
TP53	p.(R196Ter)	c.586C>T	.	chr17:7578263	49.77%	NM_000546.5	nonsense

Copy Number Variations

Gene	Locus	Copy Number
MYC	chr8:128748884	5.1

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