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Leading a new era of precision oncology

Oncofocus®

Precision Oncology

ONCOFOCUS® TEST REPORT

Oncologica UK Ltd, Suite 2, The Newnham Building,
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Table of Contents

Patient demographics

ONC19			
Surname		**Requester**	
Forename		**Contact details**	
DOB		**Date requested**	
Gender	Male		
Histology #		**Tumour %**	70-80%
Primary site	Prostate	**Tumour %**	-
Tumour subtype	Microacinar	**(macrodissected)**	
Tissue Type	Prostate		

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 748 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 4, 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
CDK12 p.(K721fs) c.2163delA	Clinical trials and/or off-label	Clinical trials and/or off-label	16

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. Please note this version of the Oncofocus test is an upgraded version to that accredited on our schedule

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Tier Criteria Met

Genomic Alteration	Tier Classification for Prostate Cancer
CDK12 p.(K721fs) c.2163delA 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

CDK12 p.(K721fs) c.2163delA

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
enzalutamide, talazoparib	✖	✖	✖	✖	● (III)
atezolizumab	✖	✖	✖	✖	● (II)
durvalumab + olaparib	✖	✖	✖	✖	● (II)
durvalumab, olaparib	✖	✖	✖	✖	● (II)
olaparib	✖	✖	✖	✖	● (II)
olaparib + testosterone cypionate, olaparib + testosterone enanthate	✖	✖	✖	✖	● (II)
pembrolizumab	✖	✖	✖	✖	● (II)
pembrolizumab + chemotherapy	✖	✖	✖	✖	● (II)
rucaparib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
VX-970	✖	✖	✖	✖	● (II)
avelumab + talazoparib	✖	✖	✖	✖	● (I/II)
BAY-1895344	✖	✖	✖	✖	● (I/II)
pamiparib + tislelizumab	✖	✖	✖	✖	● (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 Details

Current Clinical Trials Information

Clinical Trials information is current as of 2019-06-05. 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'.

CDK12 p.(K721fs) c.2163delA

NCT03395197

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Of Talazoparib With Enzalutamide In Metastatic Castration-Resistant Prostate Cancer

Cancer type: Prostate Cancer

Variant class: DNA repair mutation

Other identifiers: C3441021, EudraCT Number: 2017-003295-31, JapicCTI-194665, NCI-2018-01651, Pfizer C3441021, TALAPRO-2

Population segments: First line, Hormone refractory, Stage IV

Phase: III

Therapies: enzalutamide, talazoparib

Locations: Australia, Finland, Japan, United States

US States: AK, AZ, CA, CO, NE, NJ, NY, OH, SC, TN, UT

Contact: Pfizer CT.gov Call Center [800-718-1021; ClinicalTrials.gov_Inquiries@pfizer.com]

NCT03810105

A Phase II Study of Olaparib and Durvalumab in Men With Castration Sensitive Biochemically Recurrent Non-Metastatic Prostate Cancer Harboring Mutations in DNA Damage Repair

Cancer type: Prostate Cancer

Variant class: CDK12 deleterious mutation

Other identifier: 18-480

Population segments: First line, Hormone refractory, Stage I, Stage II, Stage III

Phase: II

Therapies: durvalumab, olaparib

Location: United States

US States: NJ, NY

Contact: Dr. Karen Autio [646-422-4632; AutioK@mskcc.org]

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CDK12 p.(K721fs) c.2163delA (continued)

NCT03012321
BRCAAway: A Randomized Phase II Trial of Abiraterone, Olaparib, or Abiraterone + Olaparib in Patients With Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects

Cancer type: Prostate Cancer

Variant class: CDK12 mutation

Other identifiers: 19137, BRCAAway, NCI-2016-01834, NU 16U05, NU_16U05, PCCTC #: c16-168, STU00203960

Population segments: First line, Hormone refractory, Stage IV

Phase: II

Therapy: olaparib

Location: United States

US States: FL, IL, IN, MD, MI, MN, MO, NC, UT, VA

Contact: Study Coordinator [312-695-1301; cancertrials@northwestern.edu]

NCT03516812
Bipolar Androgen Therapy Plus Olaparib in Patient With Castration-Resistant Prostate Cancer

Cancer type: Prostate Cancer

Variant class: DNA repair deleterious mutation

Other identifiers: 9984, NCI-2018-00542, RG1718004

Population segments: First line, Hormone refractory, Stage IV

Phase: II

Therapies: olaparib + testosterone cypionate, olaparib + testosterone enanthate

Location: United States

US State: WA

Contact: Michael T. Schweizer [206-288-6252; schweize@uw.edu]

NCT03533946
A Phase II Study of Rucaparib Monotherapy in Nonmetastatic, Hormone-Sensitive Prostate Cancer Demonstrating "BRCAness" Genotype (ROAR)

Cancer type: Prostate Cancer

Variant class: CDK12 mutation

Other identifiers: HCI111833, NCI-2018-01754, ROAR

Population segments: First line, Stage I, Stage II, Stage III

Phase: II

Therapy: rucaparib

Location: United States

US State: UT

Contact: Jill Broghammer [801-213-6232; jill.broghammer@hci.utah.edu]

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CDK12 p.(K721fs) c.2163delA (continued)

NCT03148795
TALAPRO-1: A Phase II, Open-Label, Response Rate Study of Talazoparib In Men With DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer Who Previously Received Taxane-Based Chemotherapy and Progressed on at Least 1 Novel Hormonal Agent (Enzalutamide And/Or Abiraterone Acetate/Prednisone)

Cancer type: Prostate Cancer

Variant class: DNA repair mutation

Other identifiers: 16358, C3441006, CSET 2503, EudraCT Number: 2016-002036-32, IRAS ID: 212853, MDV3800-06, MDV3800-06(C3441006), NCI-2017-01403, NL59035.091.16, TALAPRO-1

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

Phase: II

Therapy: talazoparib

Locations: Australia, Austria, Belgium, France, Hungary, Italy, Netherlands, Republic of Korea, Spain, United Kingdom, United States

US States: AZ, CA, GA, VA, WA, WI

Contact: Pfizer Pfizer CT.gov Call Center [800-718-1021; ClinicalTrials.gov_Inquiries@pfizer.com]

NCT03506997
PERSEUS1: Phase II Trial of the Immune Checkpoint Inhibitor Pembrolizumab for Patients Suffering From Metastatic Prostate Cancer

Cancer type: Prostate Cancer

Variant class: DNA repair pathway

Other inclusion criteria: MMR deficient

Other identifiers: CCR4559, EudraCT Number: 2017-000931-15, ICR-CTSU/2016/10060, IRAS ID 208952, PERSEUS1

Population segments: Hormone refractory, Second line, Stage IV

Phase: II

Therapy: pembrolizumab

Location: United Kingdom

NCT03248570
Phase II Open Label Study of Pembrolizumab in Patients With Metastatic Castration Resistant Prostate Cancer (mCRPC) With or Without DNA Damage Repair Defects

Cancer type: Prostate Cancer

Variant class: DNA repair pathway

Other identifiers: 16557, 17-22165, CC 16557, NCI-2017-02408

Population segments: Hormone refractory, Second line, Stage IV

Phase: II

Therapy: pembrolizumab + chemotherapy

Location: United States

US State: CA

Contact: Paula Dutton [877-827-3222; cancertrials@ucsf.edu]

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CDK12 p.(K721fs) c.2163delA (continued)

NCT03330405
A Phase Ib/II Study To Evaluate Safety And Anti Tumor Activity Of Avelumab In Combination With The Poly(Adenosine Diphosphate [Adp]-Ribose) Polymerase (Parp) Inhibitor Talazoparib In Patients With Locally Advanced Or Metastatic Solid Tumors

Cancer type: Prostate Cancer

Variant class: DNA repair pathway

Other identifiers: 17-687, 18-1008, 2017-0524, 34807, B9991025, EudraCT Number: 2017-001509-33, IRAS ID 235395, JAVELIN PARP MEDLEY, NCI-2017-02385, s17-01353

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

Phase: I/II

Therapy: avelumab + talazoparib

Locations: Australia, Canada, Denmark, Hungary, Russian Federation, United Kingdom, United States

US States: AR, DC, MA, MN, NY, OH, TX

Contact: Pfizer CT.gov Call Center [800-718-1021; ClinicalTrials.gov_Inquiries@pfizer.com]

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: Prostate Cancer

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]

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CDK12 p.(K721fs) c.2163delA (continued)

NCT03742895
A Phase II Study of Olaparib Monotherapy in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer

Cancer type: Unspecified Solid Tumor

Variant class: CDK12 deleterious mutation

Other identifiers: 2018-01891, 7339-002, 7339-002-00, EudraCT Number: 2018-003007-19, JapicCTI-194694, LYNK002, LYNK-002, MK-7339-002, NCI-2018-03519, SNCTP000003157

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

Phase: II

Therapy: olaparib

Locations: Argentina, Australia, Canada, Denmark, France, Guatemala, Ireland, Israel, Italy, Japan, Mexico, Peru, Republic of Korea, Russian Federation, Spain, Switzerland, Turkey, United States

US States: CA, GA, KY, MA, MI, NE, NY, OK, PA, SD, WA

Contact: Toll Free Number [888-577-8839; Trialsites@merck.com]

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: CDK12 mutation

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

Population segments: Second line, Stage III, Stage IV

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

Phase: II

Therapy: durvalumab + olaparib

Location: Australia

NCT03967938
Efficacy of Olaparib in Advanced Cancers Occurring in Patients With Germline Mutations or Somatic Tumor Mutations in Homologous Recombination Genes

Cancer type: Unspecified Solid Tumor

Variant class: CDK12 mutation

Other identifiers: 1-2018 BSMO, 1-2018BSMO, EudraCT Number: 2018-002966-37, Precision 2 - Olaparib

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

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

Phase: II

Therapy: olaparib

Location: Belgium

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CDK12 p.(K721fs) c.2163delA (continued)

NCT03718091
A Phase II Study of M6620 (VX-970) in Selected Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: CDK12 mutation

Other identifier: 18-274

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

Phase: II

Therapy: VX-970

Location: United States

US State: MA

Contact: Dr. Gregory M. Cote [617-724-4000; gcote@mgh.harvard.edu]

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

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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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.

CDK12 p.(K721fs) c.2163delA

Variant Class	Evidence Items
DNA repair pathway	4
↳ DNA repair mutation	4
↳ CDK12 mutation	5
↳ CDK12 deleterious mutation	2
↳ DNA repair deleterious mutation	1
↳ CDK12 deleterious mutation	2

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Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Allele Frequency	Transcript	Variant Effect	Gene Class	Variant Class
CDK12	p.(K721fs)	c.2163delA	.	34.15%	NM_016507.3	frameshift Deletion	Loss of Function	Deleterious

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PD-1/PD-L1 TESTING

IMMUNOFOCUS® TEST REPORT

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ONC19			
Surname		**Requester**	
Forename		**Contact details**	
DOB		**Date requested**	
Gender	Male		
Histology #		**Tumour %**	70-80%
Primary site	Prostate	**Tumour %**	-
Tumour subtype	Microacinar	**(macrodissected)**	
Tissue Type	Prostate		

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

No significant PD-L1 immunostaining of tumour cells is observed. The tumour is associated with a focal patchy PD-L1 expressing immune cell (IC) infiltrate. The PD-L1 expressing tumour infiltrating immune cells (ICs) cover <1% of the tumour area occupied by tumour cells, intratumoural and contiguous peritumoural stroma.

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

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