# An adaptive multi-arm phase II trial of maintenance targeted therapy after chemotherapy in metastatic urothelial cancer

Submission date	Recruitment status No longer recruiting	[X] Prospectively registered		
12/09/2016		[X] Protocol		
Registration date	Overall study status	Statistical analysis plan		
16/09/2016	Completed	[X] Results		
Last Edited	Condition category	[] Individual participant data		
28/12/2022	Cancer			

#### Plain English summary of protocol

http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-more-treatment-after-chemotherapy-for-advanced-urinary-tract-cancer-urothelial-cancer

# Contact information

### Type(s)

Public

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Scientific

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# Additional identifiers

Clinical Trials Information System (CTIS)

2015-003249-25

Protocol serial number

ATLANTIS\_2015

# Study information

#### Scientific Title

An adaptive multi-arm phase II trial of maintenance targeted therapy after chemotherapy in metastatic urothelial cancer

#### Acronym

**ATLANTIS** 

#### Study objectives

The trial hypothesis is that the addition of biomarker-targeted novel agents used as maintenance therapy after chemotherapy will improve clinical efficacy in patients with metastatic urothelial cancer.

### Ethics approval required

Old ethics approval format

### Ethics approval(s)

Approved 01/12/2016, West of Scotland Research Ethics Committee 1 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 3140213; WoSREC1@ggc.scot.nhs.uk), ref: 16/WX/0197

# Study design

Multi-centre randomised phase II trial

# Primary study design

Interventional

# Study type(s)

Treatment

Health condition(s) or problem(s) studied

#### Metastatic urothelial cancer

#### **Interventions**

Current interventions as of 14/07/2020:

Multiple novel agents will be tested in parallel and patients will enter into particular ATLANTIS component subgroup studies dependent on their biomarker profile. The control arm will be placebo-controlled and double blind.

#### Rucaparib drug subgroup:

Patients will receive continuous daily dosing (days 1-28 of a 28 day cycle) until progression or acceptable toxicity.

- 1. Control arm: Matched placebo 600 mg twice daily and can be taken either with food or without food
- 2. Experimental arm: Rucaparib 600 mg twice daily and can be taken either with food or without food

Dose reductions are recommended for events that, if persistent, could become serious or intolerable. The dose may be reduced (to 500 mg of rucaparib) due to treatment related toxicity. This should be clinically driven. Patients with grade 3 or 4 toxicity (as per CTCAE version 4.03) should be considered for a dose reduction, following recovery to grade 1 or baseline.

#### Enzalutamide drug subgroup:

Patients will receive continuous daily dosing (days 1-28 of a 28 day cycle) until progression or acceptable toxicity.

- 1. Control arm: Matched placebo 160 mg once daily
- 2. Experimental arm: Enzalutamide 160 mg once daily

It is rarely necessary to reduce the dose of enzalutamide. Patients who experience grade 3 or 4 toxicity (as per CTCAE version 4.03), that cannot be ameliorated by the use of appropriate medical intervention, may interrupt enzalutamide until the toxicity improves to grade 2 or lower. Subsequent dosing may be restarted at the original dose (160mg) or a reduced dose of 80mg once daily.

#### Cabozantinib drug subgroup:

Patients will receive continuous daily dosing (days 1-28 of a 28 day cycle) until progression or unacceptable toxicity.

- 1. Control arm: Matched placebo 40mg once daily in the fasted state i.e. no food for at least 2 hours before through to 1 hour after taking.
- 2. Experimental arm: Cabozantinib 40mg once daily in the fasted state i.e. no food for at least 2 hours before through to 1 hour after taking.

Dose reductions are recommended for events that, if persistent, could become serious or intolerable. The dose may be reduced (to 20mg of cabozantinib) due to treatment related toxicity. This should be clinically driven. Patients with grade 3 or 4 toxicity (as per CTCAE version 4.03) should be considered for a dose reduction, following recovery to grade 1 or baseline.

Patients will continue to receive trial drug/placebo until progression, unacceptable toxicity, start of further systemic anticancer therapy, withdrawal of consent or the investigator decides it is not in the best interest of the patient to continue. Patients will be followed up for overall

survival and further systemic anti-cancer treatments after progression has occurred. Data will be collected until 8 months after the last patient has been enrolled.

#### Previous interventions:

Multiple novel agents will be tested in parallel and patients will enter into particular ATLANTIS component subgroup studies dependent on their biomarker profile. The control arm will be placebo-controlled and double blind. The initial subgroup will investigate cabozantinib versus matched placebo at 40mg PO once daily.

#### Cabozantinib drug subgroup:

Patients will receive continuous daily dosing (days 1-28 of a 28 day cycle) until progression or unacceptable toxicity.

- 1. Control arm: Matched placebo 40 mg once daily in the fasted state i.e. no food for at least 2 hours before through to 1 hour after taking.
- 2. Experimental arm: Cabozantinib 40 mg once daily in the fasted state i.e. no food for at least 2 hours before through to 1 hour after taking.

Dose reductions are recommended for events that, if persistent, could become serious or intolerable. The dose may be reduced (to 20 mg of cabozantinib) due to treatment-related toxicity. This should be clinically driven. Patients with grade 3 or 4 toxicity (as per CTCAE version 4.03) should be considered for a dose reduction, following recovery to grade 1 or baseline.

Patients will continue to receive trial drug/placebo until progression, unacceptable toxicity, start of further systemic anticancer therapy, withdrawal of consent or the investigator decides it is not in the best interest of the patient to continue. Patients will be followed up for overall survival and further systemic anti-cancer treatments after progression has occurred. Data will be collected until 8 months after the last patient has been enrolled.

#### Intervention Type

Drug

#### **Phase**

Phase II

### Drug/device/biological/vaccine name(s)

Cabozantinib, enzalutamide, rucaparib

#### Primary outcome(s)

Progression free survival- RECIST 1.1 tumour measurements, assessed 12 weekly during trial treatment. PFS is time from randomisation until progression or death, whichever occurs first

# Key secondary outcome(s))

- 1. Overall survival follow up by local investigator
- 2. Safety and tolerability CTCAE assessment every 4 weeks whilst on study treatment
- 3. Response rate- RECIST 1.1 tumour measurements, assessed 12 weekly during trial treatment. Best response recorded from the start of treatment until disease progression
- 4. Maximum reduction in the size of measurable lesions RECIST 1.1 tumour measurements, assessed 12 weekly during trial treatment. Maximum reduction recorded from the start of treatment until disease progression

#### Completion date

17/05/2022

# Eligibility

#### Key inclusion criteria

- 1. Previously diagnosed stage IV urothelial cancer (UC) (T4b, Nany, Many; Tany, N 1-3, M0; Tany, Nany, M1) see Appendix II)
- 2. Histologically confirmed urothelial cancer. This includes cancers of the urinary bladder, ureter, renal pelvis or urethra with transitional and/or squamous histology. A component of either or both of these histologies is adequate for entry
- 3. Able to commence the trial treatment within 10 weeks of completing chemotherapy
- 4. Adequate tissue for biomarker testing. Testing will occur centrally
- 5. Patients must have received between 4 and 8 cycles of first line chemotherapy for metastatic /advanced UC to be eligible \*\*. Previous adjuvant or neoadjuvant chemotherapy does not count as a line of therapy
- 6. Adequate organ function as defined in the relevant subgroup specific appendix
- 7. ECOG performance status 0-2
- 8. Age ≥ 16 years
- 9. Female patients of childbearing potential must agree to comply with effective contraceptive measures, has been using adequate contraception since the last menses, will use adequate contraception during the trial, and has a negative pregnancy test within one week of trial entry.
- 10. Male patients with partners of child-bearing potential must agree to take measures not to father children by using one form of highly effective contraception, effective at the first administration of IMP and throughout the trial
- 11. Written informed consent prior to admission to this trial
- 12. Meets all inclusion criteria for the relevant component subgroup listed in the appendices \*\*Standard chemotherapy consists of any widely accepted regimen. Patients who have had delays in treatment or dose reductions should not be excluded, providing they received at least 4 cycles of treatment.

# Participant type(s)

Patient

### Healthy volunteers allowed

No

#### Age group

Adult

#### Sex

All

#### Total final enrolment

115

#### Key exclusion criteria

1. Progression during first-line chemotherapy for metastatic disease. This should be based on a radiological comparison between the pre-chemotherapy CT and end of treatment CT (local review). Patients may be permitted to enter the trial if their end of chemotherapy scan shows

response or stable disease (local assessment using RECIST 1.1) when compared to their latest pre-chemotherapy scan, even if there is progression when compared to a nadir scan performed during chemotherapy. These patients should be discussed with the trial team

- 2. In the opinion of the Investigator requires second line chemotherapy
- 3. More than one line of chemotherapy for metastatic or locally advanced disease (where the regimen is changed during first-line treatment without evidence of progression (for example the patient changes from cisplatin to carboplatin due to toxicity) this will constitute a single line of chemotherapy). Prior adjuvant / neoadjuvant chemotherapy is permitted in addition
- 4. Patients receiving radical/curative surgery or radiotherapy at the end of first line treatment (palliative radiotherapy is allowed but must be > 2 weeks prior to trial entry)
- 5. Patients receiving less than 4 or more than 8 cycles of chemotherapy before randomisation and initiation of trial intervention (excluding any chemotherapy given as neo-adjuvant / adjuvant) 6. Treatment with any other investigational agent within 28 days prior to first dose of trial
- 6. I reatment with any other investigational agent within 28 days prior to first dose of medication within ATLANTIS
- 7. Less than 3 or more than 10 weeks since the last infusion of first-line chemotherapy for advanced/metastatic UC at time of initiation of trial interventions
- 8. History of another malignancy in the last 2 years (other than treated squamous/basal cell skin cancer, treated early stage cervical cancer or treated / biochemically stable, organ confined prostate cancer not requiring on-going androgen deprivation therapy)
- 9. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder)
- 10. Positive pregnancy test for females
- 11. Inadequate organ function as defined in drug-specific appendices
- 12. Ongoing therapy with prohibited medication which cannot be discontinued prior to starting trial specific intervention (as defined in drug-specific appendices)
- 13. Major surgery or any radiotherapy within 3 weeks prior to trial entry (palliative radiotherapy within >2 weeks prior to trial entry is permitted)
- 14. Significant comorbidity or serious intercurrent medical or psychiatric illness, including serious active infection which, in the opinion of the investigator would make it inappropriate for the patient to enter the trial
- 15. Women who are breast feeding
- 16. Meets any of the exclusion criteria listed in the relevant component subgroup specific appendix

**Date of first enrolment** 01/11/2016

Date of final enrolment 17/05/2022

# Locations

Countries of recruitment

**United Kingdom** 

England

Scotland

Wales

# Study participating centre Beatson West of Scotland Cancer Centre

1053 Great Western Rd Glasgow United Kingdom G12 0YN

# Study participating centre Barts Health NHS Trust

W Smithfield London United Kingdom EC1A 7BE

### Study participating centre Guy's and St Thomas' Hospital

Great Maze Pond London United Kingdom SE1 7EH

# Study participating centre Southampton General Hospital

Tremona Road Southampton United Kingdom SO16 6YD

# Study participating centre The Clatterbridge Cancer Centre

Clatterbridge Health Park Clatterbridge Rd Wirral United Kingdom CH63 4JY

# Study participating centre Royal Lancaster Infirmary

Ashton Road

Lancaster United Kingdom LA1 4RP

# Study participating centre Velindre NHS Trust

2 Charnwood Court Heol Billingsley Parc Nantgarw Cardiff United Kingdom CF14 2TL

# Study participating centre The Christie Hospital

Wilmslow Road Manchester United Kingdom M20 4BX

## Study participating centre The Royal Marsden Hospital

Downs Road Sutton United Kingdom SM2 5PT

## Study participating centre St James' Hospital

Beckett Street Leeds United Kingdom LS9 7TF

# Study participating centre University College London Hospitals

250 Euston Road London United Kingdom NW1 2PG

## Study participating centre The Freeman Hospital

Freeman Road Newcastle United Kingdom NE7 7DN

# Study participating centre The Churchill Hospital

Old Road Headington Oxford United Kingdom OX3 7LE

#### Study participating centre Musgrove Park Hospital

Parkfield Drive Taunton United Kingdom TA1 5DA

### Study participating centre Nottingham University Hospital

Hucknall Road Nottingham United Kingdom NH5 1PB

# Study participating centre Aberdeen Royal Infirmary

Foresterhill Road Aberdeen United Kingdom AB25 2ZN

# Study participating centre Bristol University Hospitals

Upper Maudlin Street

Bristol United Kingdom BS2 8HW

# Study participating centre Queens Hospital Romford

Rom Valley Way Romford United Kingdom RM7 0AG

# Study participating centre Portsmouth Hospital

Southwick Hill Road Portsmouth United Kingdom PO6 3LY

### Study participating centre Leicester Royal Infirmary

Infirmary Square Leicester United Kingdom LE1 5WW

# Study participating centre Derby Hospitals

Uttoxeter Road Derby United Kingdom DE22 3NE

# Study participating centre Western General Hospital

Crewe Road S Edinburgh United Kingdom EH4 2XU

## Study participating centre Maidstone Hospital

Hermitage Lane Maidstone United Kingdom ME16 9QQ

### Study participating centre Royal Bournemouth & Christchurch Hospitals

Castle Lane E Bournemouth United Kingdom BH7 7DW

#### Study participating centre Kings Mill Hospital

Mansfield Road Sutton-in-Ashfield United Kingdom NG17 4JL

## Study participating centre Charing Cross Hospital

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# Study participating centre Derriford Hospital

Derriford Road Plymouth United Kingdom PL6 8DH

# Study participating centre Royal Preston Hospital

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# Study participating centre Shrewsbury Hospital

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# Study participating centre Royal Blackburn Hospital

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# Study participating centre Pinderfields Hospital

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# Study participating centre Weston Park Hospital

Whitham Road Broomhill Sheffield United Kingdom S10 2SJ

# Study participating centre Sunderland Royal Hospital

Kayll Road Sunderland United Kingdom SR4 7TP

# Sponsor information

#### Organisation

NHS Greater Glasgow and Clyde

#### Organisation

University of Glasgow

# Funder(s)

#### Funder type

Charity

#### **Funder Name**

Cancer Research UK

#### Alternative Name(s)

CR\_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

#### Funding Body Type

Private sector organisation

#### **Funding Body Subtype**

Other non-profit organizations

#### Location

United Kingdom

#### **Funder Name**

**Exelixis Inc** 

# **Results and Publications**

#### Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date

#### IPD sharing plan summary

Data sharing statement to be made available at a later date

# Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Rucaparib results	01/01/2023	28/12/2022	Yes	No
<u>Protocol article</u>		19/04/2020	28/12/2022	Yes	No
Abstract results	Cabozantinib results	08/06/2022	28/12/2022	No	No
Plain English results	Early results for participants in group 2	22/02/2022	23/02/2022	No	Yes
Protocol file	version 2.7	17/05/2022	21/09/2022	No	No