ISRCTN25859465 https://doi.org/10.1186/ISRCTN25859465

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

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

EudraCT/CTIS number
2015-003249-25

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
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

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

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 measure

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

Secondary outcome measures
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

Overall study start date
31/10/2016

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

Age group
Adult

Sex
Both

Target number of participants
140

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 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
England

Scotland

United Kingdom

Wales

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Rd
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United Kingdom
G12 0YN

Study participating centre
Barts Health NHS Trust
W Smithfield
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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
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SO16 6YD

Study participating centre
The Clatterbridge Cancer Centre
Clatterbridge Health Park
Clatterbridge Rd
Wirral
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CH63 4JY

Study participating centre
Royal Lancaster Infirmary
Ashton Road
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United Kingdom
LA1 4RP

Study participating centre
Velindre NHS Trust
2 Charnwood Court Heol Billingsley
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CF14 2TL

Study participating centre
The Christie Hospital
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M20 4BX

Study participating centre
The Royal Marsden Hospital
Downs Road
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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
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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
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United Kingdom
BS2 8HW

Study participating centre
Queens Hospital Romford
Rom Valley Way
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Study participating centre
Portsmouth Hospital
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Study participating centre
Leicester Royal Infirmary
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LE1 5WW

Study participating centre
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Study participating centre
Western General Hospital
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EH4 2XU

Study participating centre
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Study participating centre
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PL6 8DH

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PR2 9HT

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Mytton Oak Road
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BB2 3HH

Study participating centre
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Aberford Road
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WF1 4DG

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

Sponsor details
Clinical Research and Development
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
Scotland
United Kingdom
G3 8SW

Sponsor type
Hospital/treatment centre

Website
http://www.nhsggc.org.uk/

Organisation
University of Glasgow

Sponsor details
Clinical Research and Development
West Glasgow Ambulatory Care Hospital
Dalnair Street
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G3 8SW

Sponsor type
University/education

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Exelixis Inc

Results and Publications

Publication and dissemination plan
The ATLANTIS TMG is responsible for approving the content and dissemination of all publications, abstracts and presentations arising from the trial and for assuring the confidentiality and integrity of the trial.

Intention to publish date
31/12/2024

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?
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
Abstract results	Cabozantinib results	08/06/2022	28/12/2022	No	No
Protocol article		19/04/2020	28/12/2022	Yes	No
Results article	Rucaparib results	01/01/2023	28/12/2022	Yes	No