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

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Abstract

Background Metastatic urothelial cancer (UC) is the eighth most common cause of cancer death in the UK. Standard first-line treatment, for most patients, is cytotoxic chemotherapy. Although UC is initially sensitive to chemotherapy, relapse is almost inevitable after which outcomes are poor, with median overall survival 8 months. There is, therefore, an urgent need for novel therapies to improve outcomes for this patient group.

Methods ATLANTIS is a randomised phase II, adaptive design trial of maintenance therapy in biomarker defined subgroups of patients with advanced UC. The primary end-point is progression-free survival (PFS) and the study involves over 30 UK cancer centres.

Discussion ATLANTIS is the first study in the UK to employ a precision medicine approach to UC patients for maintenance treatment. Agents with positive efficacy signal will proceed to randomised phase III trials to confirm activity of novel biologically stratified therapies in UC.

Background

Urothelial cancer (UC) is the eighth most common cause of cancer-related death in the UK. Around 5,300 patients died from UC in the UK in 2016 (Cancer Research UK, 2017). Cytotoxic platinum-based doublet chemotherapy is routinely used for metastatic or locally advanced disease in the first line setting\(^1,2\). Although the majority of patients derive benefit, relapse is almost inevitable and occurs, on average, 4 months after completion. Once relapse has occurred, survival and quality of life are often poor with short median progression-free (PFS) and overall survival (OS) of 2 and 8 months respectively\(^3\). In recent years immune checkpoint inhibitors, which can benefit around 20% of patients with durable responses and proven survival advantage, have found a role in second line treatment after failure of platinum based chemotherapy\(^4,5\). Their role in first line treatment is currently limited to patients with high PDL-1 expression who are not suitable for platinum-based chemotherapy\(^6,7\). There are though, still a majority of patients with advanced UC who do not derive significant benefit from immune checkpoint inhibitors and whose subsequent treatment options are very limited. Second-line chemotherapy may be used, but response rates are low and benefit compared to best supportive care is uncertain, although recent data suggest that the combination of
docetaxel and the vascular endothelial growth factor targeted antibody ramucirumab may provide modest benefits in selected patients in the second line setting⁸.

There is therefore a clear need for new effective treatments for patients with advanced UC. The molecular heterogeneity of urothelial cancer suggests that patients may be well served by a precision-medicine approach. Testing new drugs in combination with first line chemotherapy is often challenging due to toxicity of combinations in this patient group⁹. Studies in the second line setting have historically been limited by the high symptom burden and poor prognosis for patients. Therefore, maintaining clinical benefit after first line chemotherapy may be an attractive way to improve outcomes for patients with advanced UC.

Maintenance therapy after first line chemotherapy is an opportunity for novel drug development in advanced UC. This was demonstrated in the UK NCRN LAMB trial, which completed accrual in 2013 having screened 520 patients and randomised 221 patients with epidermal growth factor expressing urothelial tumours from over 40 UK sites between lapatinib and placebo (NCT00949455). In this trial, lapatinib did not prolong survival or progression free survival in any of the defined subgroups, confirming observation alone as the standard of care in this patient group¹⁰. The study did reinforce the proof of concept that such a trial would be acceptable to patients and could be successfully delivered in the UK.

Methods And Study Design

ATLANTIS is a multi-centre randomised phase II signal-searching trial of targeted novel agents in biomarker-defined subgroups using an adaptive design (Figure 1). Multiple novel agents will be used in parallel and patients will be entered into ATLANTIS subgroup studies dependent on tumour biomarker profile. The control arm for each comparison will be placebo and comparison will be double-blind where possible.

Figure1. Study design for patients in ATLANTIS trial.
**Trial Population**

The target population in ATLANTIS is patients with metastatic or locally advanced urothelial cancer (T4b and/or N1-3 and/or M1) who are not being considered for radical therapy. Patients must have achieved an objective response or stable disease, according to local radiology review, after 4-8 cycles of first-line chemotherapy. Patients must be able to start maintenance treatment within the study at least 3 but no more than 10 weeks after completion of their first line of chemotherapy for metastatic or locally advanced disease. Biomarker analysis of archival tissue to determine ATLANTIS biomarker defined subgroups can occur any time after the diagnosis of UC, as long as appropriate consent has been taken.

**Study Objectives and End Points**

The principal research question is whether molecularly-targeted maintenance therapy after chemotherapy can delay the time to progression in molecularly-selected patients with advanced UC. ATLANTIS will thereby establish initial evidence of activity for the novel drug/biomarker combinations used in order to justify further phase III validation. A number of drugs will be tested, each compared to placebo or, where this is not feasible, observation alone. Treatment will be allocated based on molecularly defined subgroups of patients (where laboratory/clinical evidence to support such enrichment is clear) or in a manner that allows exploration of, or provides initial evidence for, predictive biomarkers. Of note, it is anticipated that in most cases the biomarker for a particular arm of the trial will itself be experimental and not yet prospectively validated.

The primary end point is progression-free survival (PFS). This has been chosen as it is largely objective and the majority of patients with UC display progression in accordance with RECIST 1.1 criteria. PFS is also clinically meaningful as the progression after first line chemotherapy represents the transition to the lethal stage of the disease and often the requirement for further systemic therapy.
The secondary end points in ATLANTIS are overall survival (OS), response rate, maximum percentage decrease in measurable disease, safety and tolerability. Exploratory end points are progression free survival in biomarker-defined subgroups other than those used for selection. Exploratory research hypotheses are embedded in the primary purpose of the trial. As such, all patients must provide adequate tissue for biomarker analysis prior to participation in the trial. This tissue collection will also provide a bio-resource for future research relating to UC.

The SPIRIT figure for ATLANTIS trial is shown in Figure 2.

Figure 2. SPIRIT figure: Schedule of Assessments for ATLANTIS trial

Patients should have signed and dated informed consent for pre-screening. Each patient must have signed and dated both informed consent forms for pre-screening biomarker testing and full trial screening before engaging in any trial related procedures. All screening evaluations must be completed before the patient is randomised to receive trial drug or placebo. Patient characteristics will be collected at pre-screening. These data should only be collected if they are available from data collection during the previous 6 weeks as part of standard care. No additional blood tests should be performed during pre-screening purely for the trial.

Tumour samples and all other translational samples should be sent for the attention of Charlotte Ackerman for centralised pre-screening or confirmation. If there is any tissue left from biomarker testing, it will be stored in the Orchid Tissue Bank for future translational research. Individual samples will be returned at the end of the trial on request. Samples will be processed in accordance with the ATLANTIS lab manual.

Weight, height, pulse and blood pressure
Human chorionic gonadotropin (HCG) results must be obtained and reviewed before the first dose of IMP is administered for women of child bearing potential.
Haematology including full blood count with WBC, ANC (absolute neutrophil count), platelet count and haemoglobin. Biochemistry including sodium, potassium, AST/ALT, alkaline phosphatise (AP), LDH, bilirubin, creatinine, protein and albumin.
All patients should have abdominal and pelvic CT or MRI, plus either chest X-ray (postero-anterior and lateral views) or chest CT scan. In the case of known or thoracic metastases seen on Chest X-ray, then patients must have a thoracic CT scan. Patients should have baseline scanning then every 12 weeks until week 49, following this scans should be done at the discretion of the individual clinician.
Patients who come off the trial should have tumour assessments within 4 weeks of coming off trial drug/placebo, irrespective of whether or not the patient is still being followed up for progression.
Patients who come off the trial should have tumour measurements where they have not been completed within the past 4 weeks. This includes abdominal and pelvic CT or MRI, plus either chest X-ray (postero-anterior and lateral views) or chest CT scan. In the case of known or thoracic metastases seen on Chest X-ray, then patients must have a thoracic CT scan. Patients who stop treatment for whatever reason before progressive disease is documented will continue to have scans at 12-weekly
intervals as previously. Follow-up visits after progression will continue at the investigators discretion until death. Future treatment and cause of death must be recorded on the CRF. Frequency of treatment visits will vary within the different treatment arms, please see individual IMP drug appendices for this information.

**Trial analysis plan**

The analysis for all subgroups in ATLANTIS will be on an intention-to-treat basis. Progression-free survival will be compared between the novel agent and placebo in each study arm within the context of a Cox model incorporating the baseline minimisation factors. The p-value for the observed hazard ratio will be determined from this model. If the observed PFS difference in favour of the novel agent is statistically significant at the 10% 1-sided level, this will be deemed a clear signal that a subsequent phase III trial is warranted. A result significant at the 20% 1-sided level would require further evidence in terms of improvement such as reduction in size of measurable disease. The overall study data will be reviewed by an Independent Data Monitoring Committee (IDMC). The IDMC will review toxicity, treatment delivery and compliance data. Recommendations will take into account all available data as well as formal futility comparison for PFS when half of the required events have occurred.

**Current biomarker-defined arms in ATLANTIS**

The design of ATLANTIS allows for the addition of further biomarker-defined subgroups throughout the lifetime of the trial. At initiation, ATLANTIS was exploring a single drug (cabozantinib) but other comparisons have been added since the trial began, each with associated Investigational Medicinal Product (IMP), which are:

*Cabozantinib*

There is a wide body of pre-clinical evidence supporting the relevance of hepatocyte growth factor (HGF), the ligand for MET, and vascular endothelial growth factor (VEGF) as anti-cancer targets in patients with UC\(^ {11}\). Cell line data shows that MET is associated with tumour proliferation and
growth. VEGF has also been demonstrated to be over-expressed in UC cell lines and associated with tumour proliferation. The combination of VEGF and MET inhibition is therefore an attractive field in patients with UC. Cabozantinib is a multi-kinase inhibitor including MET and VEGF. It has been demonstrated to have significant activity and is licensed in Europe to treat medullary thyroid and renal cancers. It has shown early signs of activity in an on-going phase II trial in patients with advanced UC. There is a currently a lack of data on the expression of MET or VEGF as a biomarker for cabozantinib activity. For this reason, all patients in ATLANTIS and other on-going studies have not selected patients on the basis of MET expression. Patients in this study will therefore potentially be eligible for the cabozantinib/placebo arm if their tumour does not over-express any current ATLANTIS target biomarker or they are not deemed suitable to enter a biomarker-defined arm of the study.

*Rucaparib*

There is emerging evidence of a subgroup of patients with UC exhibiting a DNA repair deficiency phenotype resulting in defects in a variety of genes including BRCA1/2, BAP1, PALB2, FANCD2 and ERCC2. These DNA repair gene defects predict for benefit following cisplatin-based chemotherapy in UC, implying that a switch to maintenance therapy strategy for PARP inhibition after prior chemotherapy may allow for enrichment of a ‘BRCA-like’ subgroup. PARP inhibition has demonstrated activity against multiple urothelial cancer cell lines and xenografts. Evidence supports development of PARP inhibitors in patients with either germline or somatic BRCA mutations and, in addition, a wider selected group with evidence of Homologous Recombination Deficiency (HRD) associated tumours. PARP inhibitors have demonstrated compelling evidence of efficacy in patients with relapsed high grade serous ovarian cancer demonstrating germline or somatic BRCA mutation. The concept of synthetic lethality was confirmed in proof-of-concept studies in patients with BRCA-associated tumours where data suggests BRCA mutation is significant but not required. This data implies that BRCA mutation and/or HRD associated UC patient subgroups would be suitable for investigation of a PARP inhibitor. Rucaparib is an orally bioavailable small molecule inhibitor of
PARP1, PARP2 and PARP3. Non-clinical evaluation of rucaparib has demonstrated potent inhibition of PARP enzymes and sensitivity to BRCA1/2 homozygous mutant cell lines. Patients in ATLANTIS whose tumour is positive for a composite ‘HRD biomarker’ of alterations to a list of relevant DNA repair genes and/or high percentage genomic loss of heterozygosity (LOH) at pre-screening will potentially be eligible to receive either rucaparib or placebo in double-blind fashion. LOH is a form of genomic alteration, associated with HRD, and is characterised by the loss of one copy of a gene or chromosomal region.

**Enzalutamide**

Previous in vivo and in vitro data have demonstrated that the Androgen Receptor (AR) is a potential anti-cancer target receptor in patients with UC. Unpublished data from tissue microarray in patients tested within the LAMB study demonstrated that 30% of UC tumours over-express the AR. This was also associated with poorer prognosis, raising potential clinical benefit of targeted agents against AR. Enzalutamide is a potent androgen receptor antagonist, which unlike earlier generations of anti-androgen therapies has no known agonistic effect on AR and is known to be active in men with prostate cancer who have previously failed conventional androgen deprivation therapy. The drug is well tolerated even with prolonged administration. Patients in ATLANTIS whose tumour is found to over-express the AR on immunohistochemical analysis will potentially be eligible to receive either enzalutamide or placebo in double-blind fashion.

**Discussion**

Recent studies of second-line therapy, particularly immune checkpoint inhibitors, in patients with UC have demonstrated a clinical benefit for a small proportion of patients. There remains, though, a need to improve outcomes for patients in this challenging disease. ATLANTIS offers a novel approach to previous studies in this arena by offering biomarker-defined selection of maintenance therapy after chemotherapy in patients with UC. The primary research question of this signal-searching multi-arm phase II study is to investigate whether targeted maintenance therapy after chemotherapy can delay the time to progression in molecularly-selected patients with UC. This would therefore establish clinically relevant evidence of activity in molecularly defined subgroups for the novel drug used. The
study design will investigate cabozantinib, enzalutamide and rucaparib in this setting, but also provide a generic framework that will allow new treatments to be introduced into the study in future with prospective stratification based around a molecular target.

There are currently no targeted therapies with proven activity in UC. Preclinical data suggests there are a number of eligible targets, but the number of randomised trials performed to test these hypotheses have been small. The reasons behind this remain unclear, but low levels of clinical activity in unselected patients in non-randomised phase II trials do not support progression to phase III trials in unselected patients with UC. Another explanation is that combination targeted therapy and standard chemotherapy is poorly tolerated in this patient population. ATLANTIS will be a leading global study in the development of personalised targeted therapy for patients with UC.

Such a positive randomised phase II study would be a significant breakthrough in UC and may lead into randomised phase III trials in both the metastatic and adjuvant setting. If a cohort of ATLANTIS is positive, it would be anticipated to lead to a randomised phase III study of maintenance therapy in the appropriately selected UC population. There is also unmet need for adjuvant therapy in patients with high-risk muscle invasive bladder cancer and a positive signal from ATLANTIS would also support a randomised phase III trial in this patient group with appropriate molecular selection.

Patients in ATLANTIS are asked to consent to collection of surplus tissue for translational research. Translational research hypotheses are embedded in the primary purpose of this trial, the aim of which is to demonstrate efficacy of predictive and appropriate drug interventions in UC. As such, all patients must provide adequate tissue for biomarker expression prior to trial participation. This will also provide a bio-resource for future research in UC.

The ATLANTIS trial reflects an exciting innovation in front line precision cancer medicine for patients with advanced urothelial cancer. The study design, with biomarker-negative arm, allows all patients who enter pre-screening to potentially be able to take part. The adaptive design also allows maximal opportunity to detect an efficacy signal and rapid inclusion of new hypotheses. The engrained translational research components have the potential to unlock some of the unanswered questions and push new frontiers in the management of this challenging disease.
Trial Status
At the time of publication, ATLANTIS is open to recruitment across 32 UK cancer centres. Trial recruitment began in November 2016 and estimated date of first cohort recruitment end date is December 2020. The current ATLANTIS protocol is version 2.2 (14th November 2017).

Abbreviations
UC Urothelial cancer PARP Poly (ADP-ribose) polymerase
PFS Progression-free survival BRCA Breast Cancer Susceptibility Protein
OS Overall Survival BAP1 BRCA-1 Associated Protein-1
PALB2 Partner and Localizer of BRCA2 IDMC Independent Data Monitoring Committee
IMP Investigational Medical Product FANCD2 Fanconi Anaemia group D2 protein
MET MET proto-oncogene AR Androgen Receptor
VEGF Vascular Endothelial Growth Factor HRD Homologous Recom
HGF Hepatocyte Growth Factor ERCC2 Excision Repair Cross-complementation Group-2

Declarations

Ethics approval and consent to participate
Ethical approval for ATLANTIS was approved by the West of Scotland Regional Ethics Service (REC) on 28th November 2016: REC reference 16/WS/0197. Informed consent will be obtained from all study participants prior to participation in any ATLANTIS trial activities.

Consent for publication
Not applicable

Availability of data and material
Not applicable

Competing interests
None of the authors listed in this manuscript have any competing interests to declare.

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Figures

Figure 1

Study design for patients in ATLANTIS trial
### Figure 2

SPIRIT figure: Schedule of Assessments for ATLANTIS trial

**Supplementary Files**

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