ATLANTIS

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

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Trial Summary

Title: AN ADAPTIVE MULTI-ARM PHASE II TRIAL OF MAINTENANCE TARGETED THERAPY AFTER CHEMOTHERAPY IN ADVANCED/METASTATIC UROTHELIAL CANCER (UC)

Background: Metastatic urothelial cancer (MUC) is the eighth most common cause of cancer death in the UK. Chemotherapy is standard treatment for MUC. Although MUC is initially sensitive to chemotherapy, patients usually relapse within 6 months of completion. The outcome, once relapse has occurred, is very poor (median overall survival 8 months). Therefore, maintaining response to chemotherapy is an attractive goal, and a good environment for testing active single agents in MUC. ATLANTIS is a multi-arm, multi-stage signal searching trial. Patients will be allocated to treatment (vs observation or placebo where possible) based on biomarker expression.

Design: ATLANTIS is a randomised phase II biomarker directed umbrella screening trial of maintenance therapy in biomarker defined subgroups of patients with advanced or metastatic urothelial cancer. The primary endpoint is progression-free survival.

The protocol consists of a generic main section plus novel drug-specific appendices. The relevant novel drug-specific appendices will be amended when each specific subgroup trial completes or when a further novel drug subgroup is introduced.

Central tissue screening for biomarker will occur prior to randomisation.

Within each drug subgroup of ATLANTIS, randomisation (1:1) will be stratified via minimisation according to:

- Cisplatin versus non-cisplatin based chemotherapy
- ECOG (0 v 1 v 2)
- Best response to first line chemotherapy (CR or PR versus SD)
- Progression during the final 3 cycles of chemotherapy
- Presence of visceral metastasis
- Presence of measurable disease at trial entry
- Investigational site

Objectives: The trial will investigate whether maintenance targeted therapy after chemotherapy, with treatment selection based on biomarker expression, delays time to progression and overall survival for patients with MUC.

Endpoints:

Primary: To compare progression-free survival (PFS) of trial drug and placebo/observation. Different drugs will be tested in different biomarker defined subgroups in an adaptive design. PFS has been chosen as the primary end-point as it is largely objective (the majority of urothelial cancer patients will display progression in accordance with RECIST1.1 criteria) and clinically meaningful - progression after first line therapy represents the transition to the lethal stage of the disease and often the requirement for further cytotoxic therapy.

Secondary: Overall survival, response rate, maximum percentage decrease in measurable disease, safety and tolerability.

Exploratory: Progression free survival in subgroups defined by biomarkers other than those used for treatment allocation.

Translational: Archival tissue, plasma and circulating tumor DNA will be stored and used for future research.

Population:

The target population for this trial is patients with previously diagnosed, locally advanced and/or metastatic, inoperable urothelial cancer (T4, N_{any}, M_{any}; $T_{any,}$ N1-3, M0; $T_{any,}$ $N_{any,}$ M1). Patients must have achieved an objective response or stable disease following at least 4 cycles of first-line chemotherapy (maximum of 8 cycles). Any widely accepted chemotherapy regimen is allowed. The regimen does not necessarily have to include cisplatin. Patients must start maintenance treatment at least 3 and no more than 10 weeks after the previous chemotherapy infusion. Biomarker analyses to identify the ATLANTIS biomarker subgroup can occur at any time after the diagnosis of advanced urothelial cancer prior to randomisation. Archival tissue should be used. Biomarker analyses will occur at a central laboratory.

Eligibility:

Main Inclusion Criteria:

- Previously diagnosed locally advanced and/or metastatic, inoperable urothelial cancer (UC) (T4, N_{any}, M_{any}; $T_{any,}$ N1-3, M0; $T_{any,}$ $N_{any,}$ M1) (see Appendix II).
- 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 required for entry.
- Able to commence the trial treatment within 10 weeks of completing chemotherapy.
- Adequate tissue for biomarker testing. Testing will occur centrally.
- 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. Previous immunotherapy is acceptable either in combination with or prior to first line chemotherapy.
- Adequate organ function as defined in drug specific appendices.
- ECOG performance status 0-2.
- Age ≥ 16 years.

  Female patients who are of childbearing potential (defined as all women who are not of 'non-child bearing potential') must agree to comply with highly effective contraceptive measures, haves been using highly effective contraception since the last menses, and will use highly effective contraception during the trial (for details of highly effective contraception see section 9.3). Evidence of non-child bearing status for women of child bearing potential will be a negative urine or serum pregnancy test within 7 days of trial entry into the main trial.

  Non-child bearing potential is defined as one or both of:

  - Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments AND for women under 50 years of age, LH and FSH levels within the postmenopausal range
  - Surgical sterilisation (bilateral oophrectomy or hysterectomy)

- Male patients with partners of child-bearing potential (defined as all women who are not of 'non-child bearing potential') must agree to take measures not to father children by using highly effective contraception, effective from the first administration of IMP and throughout the trial.

- Written informed consent prior to admission to this trial.
- Meets all inclusion criteria for the relevant component subgroup listed in the appendices.

Main Exclusion Criteria:

- 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 (by local clinical assessment) 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.
- In the opinion of the investigator requires second line systemic anti-cancer therapy.
- 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.
- Patients receiving radical/curative surgery or radiotherapy at the end of first line treatment (palliative radiotherapy is allowed).
- 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).
- Treatment with any other investigational agent within 28 days prior to first dose of trial medication within ATLANTIS.
- Less than 3 or more than 10 weeks since the last administration/ infusion of first-line chemotherapy for advanced/metastatic UC at time of initiation of trial interventions.
- 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).
- 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).
- Positive pregnancy test for females.
- Inadequate organ function as defined in drug specific appendices.
- Ongoing therapy with prohibited medication which cannot be discontinued prior to starting trial specific intervention (as defined in drug specific appendices).

- Major surgery or any radiotherapy within 4 weeks prior to trial entry (palliative radiotherapy >2 weeks prior to trial entry is permitted).
- 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.
- Women who are breast feeding.
- Meets any of the exclusion criteria listed in the relevant component subgroup specific appendix.

Novel agent specific eligibility criteria are documented in the correlating drug-specific appendix.

Treatment: Trial drug or placebo / observation.

Duration: 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, or until closure of the individual drug subgroup to which the patient is randomised

Within each drug subgroup of ATLANTIS, the primary efficacy analysis will occur after the required number of PFS events has occurred. At this point, patients in that subgroup will be unblinded. Patients may continue on trial drug depending on results and discussion with the pharmaceutical partner (where necessary).

Statistical Procedures and Sample Size: Within each drug subgroup of ATLANTIS, a randomised phase II screening design approach will be used. In each case this will be designed to detect the targeted hazard ratio with 90% power, 20% 1-sided level of statistical significance (or equivalently with 80% power at the 10% level of statistical significance). A result significant at the 10% level would strongly suggest a phase III trial should be undertaken, a result significant at the 20% level would require further supportive evidence in terms of an improvement in reduction in the size of measurable disease. The LAMB trial indicated that 85% of patients will have measurable disease at randomisation.

PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR ADDITIONAL TRIAL SUMMARY INFORMATION

Table of Contents

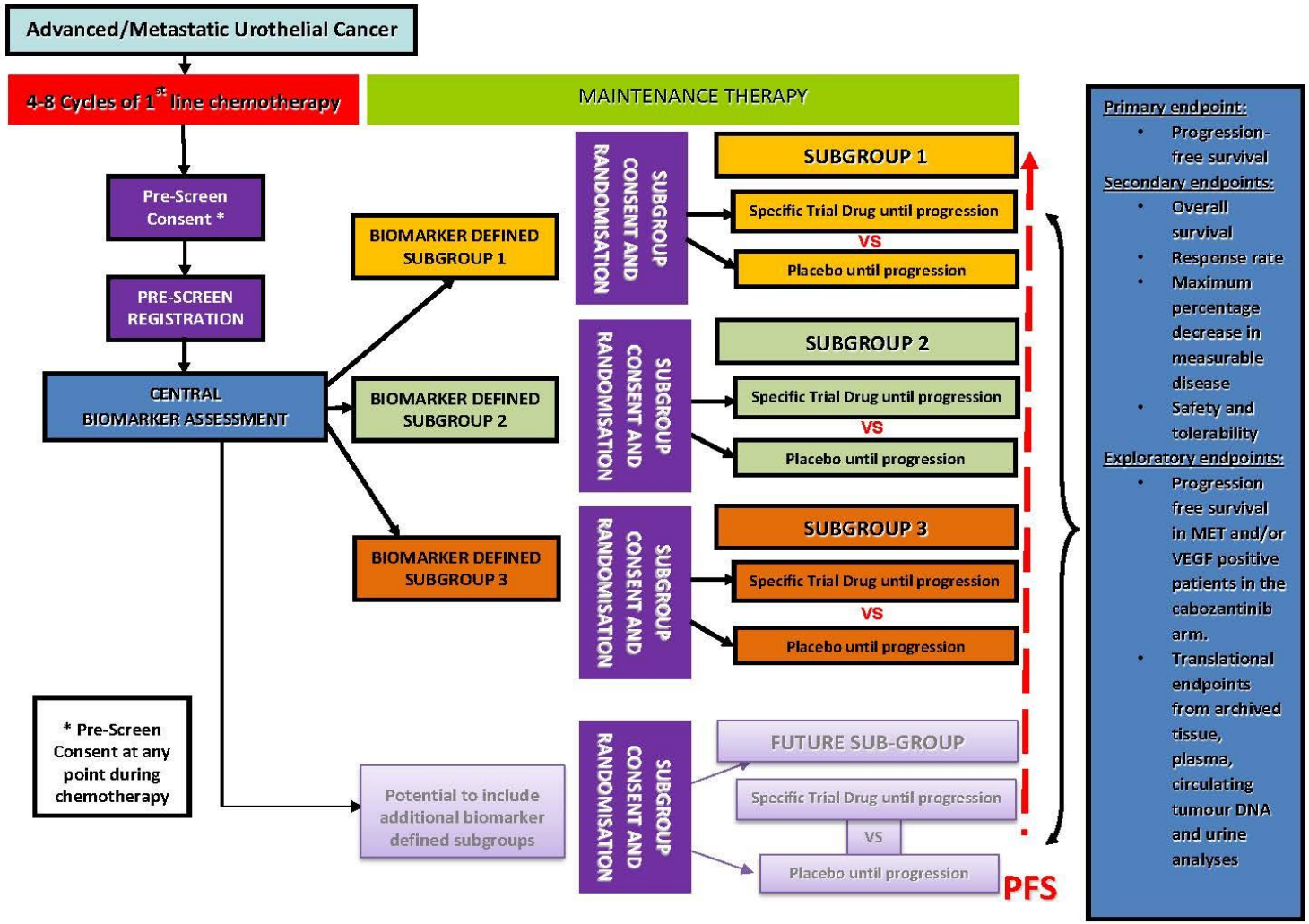
Abbreviations

ABC	Avidin-Biotin Complex
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine-aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
AR	Androgen receptor
AST	Aspartate-aminotransferase
ATP	Adenosine triphosphate
CHF	Congestive heart failure
CI	Chief Investigator
CR	Complete response
CRUK CTU	Cancer Research UK Clinical Trials Unit
CT	Computed tomography
CTA	Clinical Trials Authorisation
CTAAC	Clinical Trials Awards and Advisory Committee
CTIMP	Clinical trial investigational medicinal product
DNA	Deoxyribonucleic acid
DSUR	Development safety update report
ECG	Electrocardiogram
EGFR	Endothelial growth factor receptor
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full analysis set
FDA	Food and Drug Administration
FGFR3	Fibroblast growth factor receptor 3
FISH	Fluorescence in situ hybridization
GC	Gemcitabine and cisplatin
GCP	Good Clinical Practice
IB	Investigators Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IGFR-1	Insulin-like growth factor response 1
IHC	Immunohistochemical
IHM	Immunohistochemistry
IMP	Investigational medicinal product

IND	Investigational new drug
ITT	Intention to treat
LD	Longest diameter
LDH	Lactate dehydrogenase
LLN	Lower level of normal
LVEF	Left ventricular ejection fraction
MET	The hepatocyte growth factor receptor
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MUC	Metastatic urothelial cancer
M-VAC	Methotrexate, vinblastine, doxorubicin and cisplatin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	Non investigational medicinal product
NMR	Nuclear Magnetic Resonance
NTHA	New York Heart Association
OS	Overall survival
PD	Progressive disease
PDL-1	Programmed death ligand-1
PFS	Progression Free Survival
PI	Principal Investigator
PO	Oral administration
PPS	Per-protocol set
PR	Partial response
p-Tyr	Phosphorylated tyrosine
QLQ	Quality of life questionnaire
QOL	Quality of life
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RSI	Reference Safety Information
SAE	Serious adverse event
SD	Stable disease
SmPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TK	Tyrosine kinas
TKI	Tyrosine kinase inhibitor
TMG	Trial Management Group
UC	Urothelial cancer

UTSC	Umbrella Trial Steering Committee
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell

Trial Flow Chart



PLEASE ALSO REFER TO DRUG-SPECIFIC APPENDIX TRIAL FLOW CHART

SCHEDULE OF ASSESSMENTS

Procedure/ Assessment	Pre-Screen	Subgroup Screening		Study treatment														Follow-up	
		≤4 weeks	≤1 week	Week 1	Week5	Week9	Week13	Week 17	Week 21	Week 25	Week 29	Week 33	Week 37	Week 41	Week 45	Week 49	Week 53+	End of Treatment[13]	Off study treatment until progression[11]
Trial Procedures																			
Informed consent	X[1]	X[2]																	
Randomisation to subgroup			X																
Review of Eligibility Criteria		X																	
Demographic details	X[3]																		
Tumour characteristics and previous therapies	X[3]	X																	
Medical history		X																	
Physical examination[14]		X																X	
Smoking History		X																	
ECOG performance status	X[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[5]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[6]			X																
ECG (12-lead)		X																	
Toxicity/symptoms/ adverse events assessment	X[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments																			
Full blood count	X[3]		X[7, 15]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	

Serum biochemistry	X[3]		X[7, 15]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	
Translational blood sample	X				X[4]													X[4]	
Estimated GFR	X[3]		X																
Tumour specimen sent for central analysis [4]	X																		
Radiological Assessments																			
CT scan of chest, abdomen, pelvis		X[8]					X[8]			X[8]			X[8]			X[8]		X[9]	X[10]
Study Treatment																			
As per individual IMP drug appendix[12]				X	X	X	X	X	X	X	X	X	X	X	X	X	X		

This schedule demonstrates the minimum number of appointments for all patients within the ATLANTIS trial. Please refer to individual drug appendices for specific schedules and other visits which may be required depending on the individual IMP.

(1) Patients should have signed and dated informed consent for pre-screening.

(2) 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.

(3) 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.

(4) Tumour samples and all other translational samples should be sent 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 subject to patient consent. Individual samples will be returned at the end of the trial on request. Samples will be processed in accordance with the ATLANTIS lab manual.

(5) Weight, height, pulse and blood pressure

(6) Human chorionic gonadotropin (HCG) results must be obtained and reviewed before the first dose of IMP is administered for women of child bearing potential.

(7) Haematology including full blood count with WBC, ANC (absolute neutrophil count), platelet count and haemoglobin. Biochemistry including sodium, potassium, AST/ALT, alkaline phosphatase (AP), LDH, bilirubin, creatinine, protein and albumin.

(8) All patients should have abdominal and pelvic CT or MRI, plus CT scan of the thorax. Patients should have baseline scanning then every 12 weeks until week 49 (+/- 2 weeks), then every 16 weeks (+/- 2 weeks) to week 97 then every 24 weeks (+/- 2 weeks) during trial treatment or after completion of treatment if terminated prior to disease progression, until closure of the individual drug subgroup to which the patient is randomized.

(9) Patients who come off the trial drug 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.

(10) Patients who come off the trial drug should have tumour measurements where they have not been completed within the past 4 weeks. This includes abdominal and pelvic CT or MRI, plus chest CT scan. Patients who stop treatment for whatever reason before progressive disease is documented will continue to have scans at 12-weekly, 16-weekly or 24-weekly intervals as previously, until closure of the individual drug subgroup to which the patient is randomized.

(11) Follow-up visits after progression will continue at the investigators discretion until death, or until closure of the individual drug subgroup to which the patient is randomized. Future treatment and cause of death must be recorded on the eCRF.

(12) Frequency of treatment visits will vary within the different treatment arms, please see drug specific appendices for this information.

(13) Must be performed within 4 weeks of stopping trial treatment.

(14) Physical examination should be performed during the screening visit (within 4 weeks prior to randomisation) and at the end of treatment visit. Additional physical examinations are only required as clinically indicated.

(15) Subgroup screening laboratory determinations can be used as week 1 pre-dose blood tests as long as they are not >7 days prior to first administration of trial treatment. If >7 days prior to first administration of trial treatment then the blood tests for week 1 should be repeated.

PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR SCHEDULE OF ASSESSMENTS

1 INTRODUCTION

1.1 Overview of the current standard management of advanced/metastatic urothelial cancer

Urothelial cancer (UC), which includes cancers of the bladder, ureter, renal pelvis and urethra, is the eighth most common cause of cancer death in the UK. Around 4,900 people died from UC in 2010 in the UK (CRUK CancerStats). Cytotoxic chemotherapy is routinely used as palliative treatment for metastatic/advanced disease in the first line setting (1). Although the majority of patients who receive it initially benefit, relapse is inevitable and occurs, on average, 6 months after the completion of chemotherapy. Once relapse has occurred, survival and quality of life are poor (2). 2nd line chemotherapy may be used, but response rates are low and benefit compared with best supportive care is uncertain (3). There is no consensus about the optimal chemotherapy regimen in the 2nd line setting and progression free survival (PFS) and overall survival (OS) are short (median 2 months and 8 months respectively). Therefore, maintaining clinical benefit after first line chemotherapy may be an attractive way to improve outcomes in advanced UC (4).

There is no clear consensus on first line therapy for metastatic UC patients. This applies to patients who are eligible and those who are not eligible for cisplatin based chemotherapy. Prospective, randomised trial of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) compared with cisplatin, cyclophosphamide, and doxorubicin demonstrated improved response and median survival rates with the former regimen (5). In another multi-centre, randomised, phase III trial gemcitabine/cisplatin (GC) was compared with the M-VAC in this setting. GC yielded similar response rates, time-to-progression, and overall survival compared with M-VAC, but GC had a better safety profile and was better tolerated than M-VAC (6). Therefore in many centres GC has become the standard of care for patients with a good performance status and adequate renal function. Unfortunately, a high proportion of patients with metastatic bladder cancer have inadequate renal function or are not deemed fit enough for these cisplatin based regimens. Alternative regimens are considered in these patients. Carboplatin is commonly substituted for cisplatin in this setting with other agents such as gemcitabine or methotrexate. These regimes appear to be less efficacious than cisplatin based regimens (7-9).

The median time to progression for patients with metastatic bladder cancer is between 6 and 9 months after completion of first line chemotherapy. Subsequent treatments have been largely unsuccessful with low response rates and short progression-free intervals (8-13). The reasons for these poor results are in part related to the characteristics of the patient group at the time of

progression who, on the whole are symptomatic from their cancer and do not tolerate combination chemotherapy well. Therefore there is an urgent need to improve the treatments for patients with metastatic bladder cancer following first line chemotherapy. Interventions which maintain the duration of benefit following first line chemotherapy may be one way of meeting this need.

There is a clear need for new, effective drugs to treat urothelial cancer. The introduction of monoclonal antibodies and tyrosine kinase inhibitors (TKI's) has heralded a revolution in the management of a number of malignancies (14, 15). Unfortunately, this is not the case in urothelial cancer where there are currently few positive trials. This is despite urothelial cancer being a potentially attractive tumour type for these agents due to the over expression of a number of growth factor receptors and their ligands. Furthermore, the molecular heterogeneity of the disease suggests that patients may be well-served by a precision-medicine approach. Testing new drugs in combination with standard first line therapy has proven difficult due to the toxicity of such combinations and, by the time patients need second and subsequent lines of therapy, survival is often limited such that it can become difficult to conduct reliable trials of novel agents vs placebo in this setting.

Thus, maintenance therapy (systemic therapy after clinical benefit from first line chemotherapy) has become an opportunity for single agent drug development in advanced UC (4). For example, the UK NCRN LAMB trial completed accrual in November 2013, having screened 520 patients and randomized 221 HER 1 or 2 positive patients to either lapatinib or placebo in over 40 sites in the UK [NCT00949455]. This intervention did not prolong survival in any of the subgroups studied (Powles et al. ASCO annual meeting 2015, oral presentation) confirming that observation alone remains the standard of care in these patients. ATLANTIS is the successor trial to LAMB in the UK national portfolio. The statistical assumptions for the ATLANTIS control arm have been derived from the control arm of LAMB.

1.2 Rationale

This is a signal-searching trial. 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, thereby establishing clinically-relevant evidence of activity for the novel drugs used. A number of drugs will be tested, each compared to placebo or observation alone, either in a molecularly defined subgroup of patients (where the laboratory/clinical evidence to support such enrichment is clear) or in a manner that allows exploration of, or provides initial

evidence for, predictive biomarkers.

The trial provides a generic framework that will allow new drugs to be introduced into the trial by amendment in the future for specific biomarker identified subgroups.

In broad terms, any drug entering this trial should have a safety and tolerability profile compatible with chronic dosing in the maintenance phase.

The rationale for subgroup specific interventions together with details of prior experience in urothelial cancer and dose selection for the experimental agents can be found in the individual drug-specific appendices.

1.3 Current Experimental Agents

The experimental agents currently being tested in ATLANTIS are:

- Cabozantinib (a MET and VEGFR inhibitor, biomarker: no suitable ATLANTIS biomarker found) [see appendix V]

- Rucaparib (a PARP inhibitor, biomarker: HRD positive) [see appendix VI]

- Enzalutamide (an androgen receptor signalling inhibitor, biomarker: AR positive) [see appendix VII]

1.4 Trial Hypothesis

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

****PLEASE REFER TO DRUG-SPECIFIC APPENDICES FOR RATIONALE OF EACH BIOMARKER / DRUG****

2 TRIAL OBJECTIVES

The trial will investigate whether maintenance targeted therapy after chemotherapy, with therapy selected according to biomarker expression, extends progression free survival for patients with advanced UC.

2.1 Primary Objective

The primary objective of this trial is to:

- Compare progression-free survival (PFS) on the interventional arms to that on placebo within each biomarker/novel agent subgroup of ATLANTIS.

Each component subgroup of the trial will have a distinct statistical plan defining the numbers of patients required within that subgroup.

2.2 Secondary Objective(s)

The secondary objectives of this trial are to:

- Compare overall survival (OS) between the intervention arm and placebo for each component subgroup of the trial.
- Evaluate the safety and tolerability of the regimens in this population.
- Compare the best response rate (RR) between the intervention arm and placebo for each component subgroup of the trial.
- Compare the maximum reduction in the size of measurable lesions between the study arms.

2.3 Exploratory Objectives

- Investigate the correlation of outcome with different levels of biomarker expression, where possible.
- To collect archival tissue specimens for future biomarker testing
- To collect blood samples for future biomarker analysis

3 TRIAL DESIGN

A multi-centre, randomised phase II trial of targeted novel agents in multiple biomarker defined subgroups using an adaptive design. Multiple novel agents will be tested in parallel and patients will enter into particular ATLANTIS component subgroup studies dependant on their biomarker profile. The control arm will be placebo-controlled and double blind where possible. Where this is not possible, then the control arm will be open-label observation control. The precise nature of the control intervention is defined in the relevant subgroup specific appendix. Secondary endpoints, specific eligibility criteria and trial related procedures may also differ between different component subgroups.

Patients with an objective response or stable disease compared to baseline upon completion of first-line chemotherapy will be randomised to maintenance therapy or placebo / observation. Subgroup allocation will depend on the biomarker expression of their tissue. Biomarkers can be measured at any point from the diagnosis of metastatic / inoperable UC. Randomisation and initiation of trial intervention must occur within 10 weeks of the last administration/ infusion of chemotherapy. If multiple biomarker arms are enrolling concurrently, the prioritisation process of drug subgroup allocation will be decided in advance by the Trial Management Group. If a patient is ineligible to enter the primary allocated subgroup, it may be possible for them to enter another subgroup if they meet the relevant eligibility criteria defined in the subgroup specific appendix.

This trial will be performed according to the UK Policy Framework for Health and Social Care 2017 (as amended) and The Medicines for Human Use (clinical trials) Regulations, 2004 SI 2004:1031 (as amended). All investigators and key trial personnel will be appropriately trained in Good Clinical Practice (GCP).

3.1 Trial Population

The target population for this trial is patients with previously diagnosed metastatic or locally advanced urothelial cancer with locally advanced and/or metastatic, inoperable urothelial cancer (T4, N_{any}, M_{any}; $T_{any,}$ N1-3, M0; $T_{any,}$ $N_{any,}$ M1). Patients must have achieved an objective response or stable disease with at least 4 cycles of first-line chemotherapy (maximum of 8 cycles). Any widely accepted chemotherapy regimen is allowed. The regimen does not necessarily have to include cisplatin. Patients must start trial treatment at least 3 and no more than 10 weeks after the last chemotherapy administration/infusion of their first-line regimen. Biomarker analysis to determine ATLANTIS biomarker defined subgroups can occur any time after the diagnosis of

advanced urothelial cancer prior to randomisation as long as appropriate pre- screening consent has been taken. Archival tissue should be used. Biomarker analysis will occur centrally.

3.2 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the trial **in addition to those stated in the allocated subgroup specific appendix:**

- Previously diagnosed locally advanced and/or metastatic, inoperable urothelial cancer (UC) (T4, N_{any}, M_{any}; $T_{any,}$ N1-3, M0; $T_{any,}$ $N_{any,}$ M1) see Appendix II).
- 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 required for entry.
- Able to commence the trial treatment within 10 weeks of completing chemotherapy.
- Adequate tissue for biomarker testing. Testing will occur centrally.
- 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. Previous immunotherapy is acceptable either in combination with or prior to first line chemotherapy.
- Adequate organ function as defined in the relevant subgroup specific appendix.
- ECOG performance status 0-2.
- Age ≥ 16 years.
- Female patients who are of childbearing potential (defined as all women who are not of 'non-child bearing potential') must agree to comply with highly effective contraceptive measures, have been using highly effective contraception since the last menses, and will use highly effective contraception during the trial (for details of highly effective contraception see section 9.3). Evidence of non-childbearing status for women of childbearing potential at entry to the main trial will be a negative urine or serum pregnancy test within 7 days of entry into the main trial.

  Non-child bearing potential is defined as one or both of:

  - Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments AND for women under 50 years of age, LH and FSH levels within the postmenopausal range
  - Surgical sterilisation (bilateral oophorectomy or hysterectomy)

- Male patients with partners of child-bearing potential (defined as all women who are not of 'non-child bearing potential') must agree to take measures not to father children by using highly effective contraception, effective from the first administration of IMP and throughout the trial.
- Written informed consent prior to admission to this trial.
- 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.*

3.3 Exclusion Criteria

Patients meeting any of the following exclusion criteria or **any of those stated in the relevant subgroup specific appendix** are not to be enrolled in the trial:

- 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 (by local clinical assessment) 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.
- In the opinion of the Investigator requires second line systemic anti-cancer therapy.
- 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.
- Patients receiving radical/curative surgery or radiotherapy at the end of first line treatment (palliative radiotherapy is allowed but must be $\geq$ 2 weeks prior to trial entry).
- 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).
- Treatment with any other investigational agent within 28 days prior to first dose of trial medication within ATLANTIS.

- Less than 3 or more than 10 weeks since the last administration/infusion of first-line chemotherapy for advanced/metastatic UC at time of initiation of trial interventions.
- 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).
- 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).
- Positive pregnancy test for females.
- Inadequate organ function as defined in drug-specific appendices.
- Ongoing therapy with prohibited medication which cannot be discontinued prior to starting trial specific intervention (as defined in drug-specific appendices).
- Major surgery or any radiotherapy within 3 weeks prior to trial entry (palliative radiotherapy >2 weeks prior to trial entry is permitted).
- 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.
- Women who are breast feeding.
- Meets any of the exclusion criteria listed in the relevant component subgroup specific appendix.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR ADDITIONAL INCLUSION/EXCLUSION CRITERIA*****

In the event that a patient has a biomarker profile that means they are potentially suitable for more than one component subgroup, and they are not eligible for the initially allocated subgroup, then they may be considered for another subgroup on discussion with the Chief Investigator(s) or their delegate.

There will be no exception to the eligibility requirements at the time of registration/randomisation. Queries in relation to the eligibility criteria should be addressed via contact with the CRUK Glasgow CTU prior to registration/randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply.

3.4 Identification of participants and consent

Patients may be identified at any point after the diagnosis of metastatic or inoperable UC by their usual care team. It is anticipated that most patients will be identified at the point of initiation of first line chemotherapy for advanced disease. To permit timely delivery of biomarker results it is recommended that consent and registration to pre-screening for biomarker status takes place prior to completion of chemotherapy, ideally early on in the course of chemotherapy. There is a separate information sheet and consent form for this part of the trial. Consent and randomisation to the maintenance trial will then take place after completion of chemotherapy when on-going clinical benefit is known. The patient will be given sufficient time to consider the written patient information sheet at each stage and given an opportunity to ask questions with a member of the investigative team before signing a written consent form.

3.5 Participant Entry

Prior to commencing any trial related procedures, all participants will be fully informed about the risks, benefits and procedures involved in trial participation, and will sign a consent form confirming this process.

3.6 Registration to Pre-Screening for Biomarker Status

Once consented to the pre-screening stage of the trial, patients should be registered to allow for central tissue evaluation for biomarker testing. Patients must be registered using the pre-screening registration form provided and by contacting the Cancer Research UK Clinical Trials Unit, Glasgow (see contact details in section 3.7). A patient pre-screening number will be allocated at this point. Biomarker testing will be performed to confirm the appropriate component subgroup that the patient should be assigned to (see section 4.1). Sites will be notified by the Cancer Research UK Clinical Trials Unit, Glasgow of the biomarker testing results and the primary allocated component subgroup.

3.7 Randomisation to the Trial Following Biomarker Testing

If patients are still potentially eligible following biomarker testing, they will be offered consent into the maintenance trial. Once they have given written informed consent they will undergo a further period of screening for the trial and will proceed to randomisation, providing all other inclusion/exclusion criteria have been met. Those who are eligible will be assigned to the appropriate subgroup based upon biomarker results (see current ATLANTIS subgroup appendices).

Patients will then be randomised within the subgroup to receive the relevant trial drug or the specified control (either placebo or observation alone, depending on the specific subgroup). If the patient is not eligible for the initially-allocated subgroup, then it is possible that they may still be eligible for randomisation to another subgroup if eligible. In this situation, the next prioritised subgroup will be determined according to the patient's biomarker profile in a priority order guided by the Chief Investigators / their delegate.

Patients will not be able to be registered for pre-screening or randomised to the trial and start protocol treatment until the site has been activated to begin recruitment.

When the patient's eligibility has been confirmed, and consent forms and randomisation forms have been completed, site staff must contact the Cancer Research UK Clinical Trials Unit, Glasgow to randomise the patient to the trial. Randomisation to the trial can be done by either telephone on the following numbers:

Pre-screening Registration and Randomisation Service

Telephone Number: 0141 301 7467

Opening Hours: **Monday-Thursday 08.30-17.00**
Friday 08.30-16.30

The site will be informed of the randomisation by telephone or email.

Within each drug subgroup of ATLANTIS, randomisation (1:1) will be stratified via minimisation according to:

· Cisplatin versus non-cisplatin based chemotherapy
· ECOG (0 v 1 v 2)
· Best response to first line chemotherapy (CR or PR versus SD)
· Progression during the final 3 cycles of chemotherapy
· Presence of visceral metastasis
· Presence of measurable disease at trial entry
· Investigational site

Each patient randomised will be allocated a unique patient identifier and will be allocated a study arm or a study drug code (for blinded studies).

The participant's GP will be informed of their involvement in the trial.

3.8 Withdrawal

3.8.1 Withdrawal of Patients from Trial Treatment Alone

Patients have the right to withdraw from trial treatment at any point for any reason, without prejudice to their medical care. Similarly, the investigator may withdraw patients from the trial drug for any of the following reasons:

- Significant intercurrent illness which make it unsafe for the patient to continue trial medication
- Occurrence of any grade 4 non-haematological toxicity or an unacceptable adverse event which is attributed to the trial medication
- Treatment delay >4 weeks because of toxicity
- Patient request
- Significant non-compliance with trial treatments or activities
- General or specific changes in the patient's condition which are considered unacceptable for further treatment in the judgment of the investigator
- Progressive disease as defined by RECIST 1.1 (see appendix IV).
- Pregnancy

If a patient withdraws from treatment prior to disease progression, this information should be recorded on the Future Treatment Electronic Case Report Form (eCRF) and in the patient's medical records. At the time of withdrawal, all trial procedures outlined for the end of trial visit should be completed. Individuals who stop treatment prior to progression should be followed up with imaging as per protocol to assess time to progression. All patients should be followed up until resolution of treatment related adverse events where appropriate and SAEs require to be reported.

3.8.2 Withdrawal from all Trial Procedures

The patient may decide to withdraw from all trial procedures at any time. The investigator also has the right to withdraw patients from the trial if he/she feels that it is in the best interests of the

patient. Full details of the reasons for withdrawal should be recorded on the relevant eCRF and recorded in the patient's medical records. If a patient withdraws during the treatment phase this information should be recorded on the Future Treatment eCRF and the patient's medical record. However, SAEs will continue to require to be reported. Withdrawn patients should be followed-up in accordance with the protocol where possible and where the patient permits. If a patient withdraws from treatment and withdraws their consent for follow-up, this must be recorded in the patient's medical records and clearly document what the patient is withdrawing from. A Consent Withdrawal Form may also be completed by the site staff after discussion with the Cancer Research UK Clinical Trials Unit.

If the patient withdraws consent for the use of any data gathered on or after the date of withdrawal no further follow up data will be collected. However, if the patient experiences a SAE related to trial participation then this should be reported for the safety of all trial participants. The patient may also choose to withdraw consent for any previously collected data to be used, however safety data previously collected will be retained. Where it is possible to identify discrete bio-samples relating to that patient, they will be removed and destroyed or returned as appropriate. It may not always be possible to identify discrete individual patient samples in this way (e.g. where the sample has been anonymised, or where the sample has been included in a tissue micro-array). In such cases the patient will not be able to withdraw consent for further analysis of these samples.

4 TRIAL SCHEDULE

4.1 Pre-Screening for Biomarker Status

Patient characteristics will be collected at pre-screening. These should only be collected if they are available from data collected as part of standard of care. These will include:

- ECOG Performance status
- Estimated glomerular filtration rate (Cockcroft-Gault/Wright formula)
- Tumour characteristics and previous therapies
- Haemoglobin, serum creatinine and serum albumin

All patients who consent to pre-screening irrespective of whether or not they enter the main trial will have their best response to first line chemotherapy (as determined by the investigator, using RECIST 1.1 where these data are routinely available) and overall survival collected. Collection of

these data will occur on an annual basis until the patient has died, or until closure of the individual drug subgroup to which the patient is randomised. Patients who fail screening and are not randomised into one of the individual drug subgroups will have overall survival collected until closure of all drug subgroups.

4.1.1 Central Tissue Evaluation for Biomarker Status (and tissue storage for future translational research)

Patient eligibility must include central tissue evaluation for biomarker expression. The biomarkers to be tested may vary according to protocol amendments and are specified in the drug specific appendices.

Patients will also be asked to consent to allow their samples to be used for future cancer research.

For all patients, central tissue evaluation for biomarker expression must be performed at the ATLANTIS central laboratory, Barts Cancer Institute. Paraffin embedded blocks are preferred, but if they are unavailable, a maximum of 10 unstained sections on charged slides should be sent. The samples should include tissue from the primary tumour as well as metastatic sites if possible.

Immediately following pre-screening registration with the CRUK Glasgow CTU (see section 3.6), tumour samples should be sent to the ATLANTIS Central Laboratory for the attention of Sakunthala Kudahetti, Orchid Tissue Bank Manager at Barts Cancer Institute (address below), for centralised evaluation or confirmation. Results of the central testing will be emailed from CRUK Glasgow CTU to the participating site within 15 working days of the tumour being received at the central laboratory.

The sample must arrive at the ATLANTIS central laboratory a minimum of 3 weeks prior to main study randomisation date to allow for the results to be generated. Please send the tissue sample immediately after obtaining the pre-screening patient trial identifier from the CRUK Glasgow CTU.

Sakunthala Kudahetti ATLANTIS Trial
Orchid Tissue Bank Manager
Molecular OncologyBarts Cancer Institute
John Vane Science Centre
Charterhouse Square, London, EC1M 6BQ

Tel: 0207 882 3739

Further details are provided in the ATLANTIS laboratory manual.

If there is any additional tissue left from biomarker testing, it will be stored in the Orchid Tissue Bank for future translational research, subject to consent. Individual samples will be returned at the end of the trial on request. If required, please contact the ATLANTIS Central Laboratory at the details above.

4.1.2 Translational Blood Samples at Pre-Screening

A whole blood sample (7- 10mls) for translational research will be taken. This will include material for germ-line genetic analysis. Where possible, the samples should be taken before the patient starts any anti-cancer treatment, including any chemotherapy given as first line treatment.

Samples will be processed in accordance with the ATLANTIS laboratory manual.

4.2 Screening Procedures Prior to Participation in the Maintenance Trial

Each patient must have signed and dated an informed consent form prior to screening for a drug subgroup and before engaging in any trial related procedure. All screening evaluations must be complete before the patient is randomised to receive a trial drug or placebo.

The following procedures will be evaluated at the randomised trial screening visit:

- Clinical assessments within 4 weeks prior to trial entry:
    - Complete medical history including diagnosis of urothelial cancer, co morbidities, medications and their indications
    - Toxicity/symptoms evaluation

- Physical examination
- Vital signs (pulse, blood pressure, temperature)
- ECOG Performance status
- Smoking history

- Laboratory determinations within 7 days prior to trial entry:
  - Haematology including full blood count with WBC (white blood count), ANC (absolute neutrophil count), lymphocyte count, platelets count and haemoglobin
  - Biochemistry including AST/ALT, AP, LDH, bilirubin, creatinine, protein and albumin
  - Pregnancy test (if the patient is of childbearing potential)
  - Other safety laboratory tests as specified in subgroup specific appendix

  The above screening laboratory determinations can be used as week 1 pre-dose blood tests as long as they are not >7 days prior to first administration of trial treatment. If >7 days prior to first administration of trial treatment then the blood tests for week 1 should be repeated.

- Cardiac assessments within 4 weeks prior to trial entry:
  - ECG (12 lead)

- Tumour assessment within 4 weeks prior to trial entry:
  - Chest CT-scan.
  - Abdominal and Pelvic CT-scan or MRI.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR DRUG SPECIFIC TRIAL PROCEDURES (INVESTIGATIONS/ASSESSMENTS)*****

4.3 Progression-Free Period Procedures

4.3.1 Procedures at each visit on trial drug/placebo (may be 3 or 4 weekly – please check drug-specific appendix)

The following assessments should be performed at each visit whilst the patient receives trial drug/placebo:

- Clinical assessments:

- Toxicity/symptoms evaluation
- Physical examination (if clinically indicated)
- Vital signs including pulse, blood pressure, temperature
- ECOG Performance status
- Concomitant medications

- Laboratory determinations (**within 72 hours prior to visit**):
  - Haematology including full blood count with WBC, ANC, lymphocyte count, platelets count and haemoglobin
  - Biochemistry including AST/ALT, AP, LDH, bilirubin, creatinine, protein, albumin
  - Other safety laboratory tests as specified in relevant drug specific appendix

  - At week 5 visit only
    - Whole blood sample (7- 10mls) for translational research

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR DRUG SPECIFIC TRIAL PROCEDURES (INVESTIGATIONS/ASSESSMENTS)*****

4.3.2 Radiological Investigations

The following assessments should be performed every 12 weeks (+/- 2 weeks) from start of treatment to week 49 then every 16 weeks (+/- 2 weeks) to week 97 then every 24 weeks (+/- 2 weeks) during trial treatment or after completion of treatment if terminated prior to disease progression:

- Tumour measurements:
  - Chest CT-scan.
  - Abdominal and Pelvic CT-scan or MRI.

Note that these investigations should continue as scheduled even if treatment has ceased, or in the event of dose delays.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR DRUG SPECIFIC TRIAL PROCEDURES (INVESTIGATIONS/ASSESSMENTS)*****

4.4 End of Trial Procedures

The following assessments should be made within 4 weeks of coming off trial drug/placebo irrespective of whether or not the patient has already progressed:

- Clinical assessments:
  - Toxicity/symptoms evaluation
  - Physical examination
  - Vital signs including pulse, blood pressure, temperature
  - ECOG Performance status

- Laboratory Determinations:
  - Haematology including full blood count with WBC, ANC, lymphocyte count, platelets count and haemoglobin
  - Biochemistry including AST/ ALT, AP, LDH, bilirubin, creatinine, protein, albumin
  - Other safety laboratory investigations as specified in relevant subgroup-specific appendix
  - Whole blood sample (7.5mls) for translational research

- Tumour measurements (where these have not been performed in the 4 weeks prior to discontinuation):
  - Chest CT-scan.
  - Abdominal and Pelvic CT-scan or MRI.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR DRUG SPECIFIC TRIAL PROCEDURES (INVESTIGATIONS/ASSESSMENTS)*****

4.5 Follow-Up Visits

Follow up visits after progression will continue at the investigator's discretion until death. Future treatment and cause of death must be recorded on the eCRF. Collection of these data will occur on an annual basis until the patient has died, or until closure of the individual drug subgroup to which the patient is randomised..

Patients who stop treatment for whatever reason before progressive disease is documented, will continue to have scans as specified in section 4.3.2 until there is evidence of disease progression, or until closure of the individual drug subgroup to which the patient is randomised.

PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR DRUG SPECIFIC TRIAL PROCEDURES (INVESTIGATIONS/ASSESSMENTS)

5 TRIAL ENDPOINTS

5.1.1 Primary Endpoints

The primary endpoint is progression-free survival (PFS). This has been chosen as it is largely objective (the majority of urothelial cancer patients will display progression in accordance with RECIST1.1 criteria) and clinically meaningful as the progression after first line therapy represents the transition to the lethal stage of the disease and often the requirement for further cytotoxic therapy. It is also largely independent of the effect of subsequent therapy.

5.1.2 Secondary Endpoints

The secondary endpoints are overall survival, response rate, maximum percentage decrease in measurable disease, safety and tolerability.

5.1.3 Exploratory Endpoints

The exploratory endpoints are progression free survival in subgroups defined by biomarkers other than those used for patient selection and other translational endpoints from archived tissue, plasma and circulating tumour DNA analyses.

5.2 Translational Laboratory Tests

For handling and shipping instructions please consult the ATLANTIS laboratory manual.

6 TREATMENTS

Investigational Medicinal Products (IMP) and non-IMPs are defined in each drug-specific appendix.

Patients who are eligible for this trial will be assigned to the appropriate subgroup based upon biomarker results. Patients will then be randomised within the subgroup they are assigned, to receive either the relevant trial drug or the specified control (either placebo or observation).

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR CORRESPONDING TREATMENT SECTION*****

6.1 Trial Treatment Recording

Reasons for any dose delays, dose reductions and dose omissions of trial drugs should be documented in the appropriate section of the eCRF and in the patient's medical records. Tablet counts (where relevant) will be performed and recorded for each trial visit to assess compliance. Patients should be advised to return empty and part used bottles of oral IMP to pharmacy (for accountability requirements) at their next trial visit.

6.2 Concomitant Therapy

All concomitant therapy taken at any point from 4 weeks before drug subgroup randomisation up to and including the end of treatment visit will be documented in the appropriate section of the eCRF and in the patient's medical records along with dose, frequency and therapeutic indication. Additionally, any diagnostic, therapeutic or surgical procedure performed during the trial period, should be recorded including the date, indication, description of the procedures(s) and any clinical findings.

Patients who are offered a COVID-19 vaccine should proceed with vaccination as per local guidelines for the administration of COVID-19 vaccination in patients who are on systemic anti-cancer treatment. Vaccination with the inactivated seasonal flu vaccine is also permitted.

<u>COVID-19 treatments</u>

There is limited data available at the current time on interactions with medicines for treatment of acute COVID-19 infection and the clinical management in this therapeutic area is also rapidly evolving as new medicines are approved for use by local/national treatment guidelines. It is therefore not possible to comprehensively rule out the potential for clinically significant interactions between the study IMPs with current or future medicines for the acute treatment of COVID-19 and a pragmatic approach is required. Medicines for acute COVID-19 infection should not be unnecessarily withheld and participants should be managed wherever possible in line with local/national clinical guidelines for this patient group. The decision to follow a particular

management plan for acute COVID-19 infection, which may include the temporary withdrawal of the IMP (should this be in the participant's best interest), is at the treating physician's discretion. Investigators should refer to the protocol and current study IMP SmPC or IB for detailed information on known mechanisms for pharmacokinetic/pharmacodynamics interactions as well as the relevant COVID-19 treatment SmPC (or equivalent) to inform management decisions. Any mitigations, such as additional patient monitoring, must be documented in the participant's medical notes.

Further ad-hoc advice can also be obtained from the Sponsor/Chief Investigator and https://www.covid19-druginteractions.org/. Investigators must be vigilant at all times to the possibility of interactions and report in line with protocol pharmacovigilance requirements. Concomitant use of other medicines for COVID-19 must be recorded in the participant's CRF. Investigational treatments for acute COVID-19 treatment are not permitted without prior approval from the sponsor.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR ADDITIONAL CONCOMITANT THERAPY GUIDANCE *****

6.3 Prohibited Therapy

- Any investigational agent other than the IMP included in this protocol for the subgroup the patient is recruited to.
- Patients will not receive any other anticancer treatment including cytotoxic, hormonal or specific immune therapy whilst in the treatment phase of ATLANTIS. Single dose intravesical mitomycin will be permitted should a patient develop non-muscle invasive urothelial cancer (see section 6.11.1 for further details).
- In some cases it may be permitted for patients to receive palliative radiotherapy.

Each case should be discussed with the Chief Investigators prior to any non-trial anticancer treatment being administered.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR ADDITIONAL PROHIBITED THERAPY GUIDANCE *****

6.4 Interactions with other medications

Please see drug-specific appendices for advice about drugs which are contra-indicated in combination with the relevant trial medications.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR GUIDANCE ON INTERACTIONS WITH OTHER MEDICATIONS*****

6.5 Dose Modifications for Toxicity

*****PLEASE REFER TO DRUG SPECIFIC APPENDIX FOR GUIDANCE ON DOSE MODIFICATIONS *****

6.6 Emergency Unblinding

*****THIS SECTION RELATES ONLY TO ATLANTIS SUBGROUPS WHERE A PLACEBO IS BEING USED. PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR FURTHER GUIDANCE ON EMERGENCY UNBLINDING *****

Unblinding of patient's trial drug is strongly discouraged during the trial as blinding is critical to the integrity of the trial. Emergency unblinding may only take place in situations where the safe management of the patient's medical condition necessitates immediate knowledge of the trial medication by the person(s) responsible for the patient's care. It should be borne in mind that, unless there is a specific antidote for the trial drug, cessation of treatment without breaking the blind may be sufficient to enable management of the patient. The blind for that subject may be broken by the local Principal Investigator, responsible pharmacist or a member of staff delegated to request this. It will be the individual site's responsibility to ensure 24 hour access to unblinding is available to all staff that may have to perform this function.

The trial allocation will only be revealed to individuals on a "need to know" basis and should never be revealed to the trial statistician (apart from after the final trial analysis).

A Principal Investigator treating a patient on trial has the primary right to decide to break the blind for an individual trial subject if he or she feels that emergency unblinding is necessary. Where emergency unblinding is being considered, the local investigator should discuss the case with the trial CI or their designated deputy whenever it is practical to do so. However, in an emergency situation this may not be possible. Before breaking the blind for an individual subject, the local investigator should have determined that the information is necessary, i.e. that it will alter the patient's immediate management. In many cases, stopping the IMP without unblinding may be the appropriate management. For any treatment unblinding, the reason for decision to unblind and parties involved must be documented in the patient's medical records and on the patient's CRF. Treatment identification information should be kept confidential and should be disseminated only to those individuals that must be informed for medical management of the patient.

The CRUK Glasgow CTU must be notified of all emergency unblinding events. A log documenting all emergency unblinding throughout the duration of the trial will be maintained at the CTU.

All Principal Investigators, responsible pharmacists or a member of staff delegated to request this will have access that allows them to break the blind for an individual patient in an emergency situation as described above.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR FURTHER GUIDANCE ON EMERGENCY UNBLINDING *****

6.7 Unblinding at the point of radiological progression (if applicable)

There are no plans to permit unblinding at the point of radiological progression as all patients will discontinue trial medication at this point irrespective of allocation and there will be no planned crossover.

6.8 Unblinding Following Final Analysis

At the time of completion of the final analysis of any given subgroup, all patients in that subgroup will be unblinded and the sites informed of their treatment allocation. Availability of continued trial medication beyond this point will be specified in the subgroup specific appendices.

6.9 Unblinding for SUSARs

In the event of any SUSARs, the CRUK Glasgow CTU Pharmacovigilance team will have access to the trial allocation in order to submit an unblinded SUSAR report to the Regulatory Authorities, REC and Sponsor.

6.10 Participation in concurrent clinical trials

In general patients should not participate simultaneously in more than one trial, with the following exceptions:-

- Patients will be permitted to take part in observational research at any time whilst participating in this trial
- Patients who have progressed can enter a trial of subsequent treatment

If an exception is added to the above general criteria the Principal Investigator seeking the exception should seek approval from the Chief Investigator and Trial Management Group prior to enrolling the patient in the other trial. In such exceptional cases, it is imperative that the Sponsor(s) of both studies also approve co-enrolment within their trial.

6.11 Duration of Trial Participation

Patients remain on trial until the required number of PFS events for the primary analysis has been observed in their biomarker/trial drug subgroup or if an analysis shows that the trial drug is unlikely to show a significant benefit to patients. Patients may be removed from the trial if, in the clinician's judgement, the trial is no longer in their best interest.

6.11.1 Duration of Trial Treatment

Trial treatment should continue until any of the following have occurred:

- Disease progression as defined by RECIST1.1
- Unacceptable toxicity
- Patient withdrawal of consent for continued treatment
- Patient withdrawal of consent from the trial
- Investigator considers it is no longer in the patient's best interests to continue on trial treatment
- Commencement of another systemic anti-cancer therapy (palliative radiotherapy is permitted). Please see section 6.3.

For clarity, if a patient develops non-muscle invasive urothelial cancer then this will not constitute disease progression and the patient may continue trial treatment if it is considered safe and appropriate to do so. Single dose intravesical mitomycin will be permitted under these circumstances although prolonged courses of intravesical chemotherapy or BCG will not be permitted while the patient remains on trial medication.

6.11.2 Duration of Trial Follow-up

Follow up will continue as outlined until death, or until closure of the individual drug subgroup to which the patient is randomised.

7 ASSESSMENT OF SAFETY

Measures for patient safety include adverse event reporting and assessments as outlined in the schedule of assessments. These include assessing clinical and laboratory parameters. If a patient develops adverse events during the trial period, additional assessments will be carried out as clinically appropriate.

8 TRANSLATIONAL RESEARCH

Translational research hypotheses are embedded in the primary purpose of this trial, the aim of which is to demonstrate the efficacy of predictive biomarkers and appropriate drug interventions in UC. 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. In addition patients will be asked to donate blood samples which will be stored to permit future exploratory translational research relating to UC and / or the activity / toxicity of the drugs under trial. Samples will be processed in accordance with the ATLANTIS laboratory manual.

Access to these bio resources will be open to all investigators in the trial and other researchers. Independent oversight of applications and permissions granted is provided by the Trials Steering Committee.

9 SAFETY REPORTING

9.1 DEFINITIONS

These definitions apply to all trial participants from pre-screening consent.

9.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

9.1.2 Adverse Reaction (AR)

An adverse reaction (AR) is any untoward and unintended occurrence in a subject to whom a medicinal product has been administered which is thought to be caused by or related to that product.

9.1.3 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any of the following, whether or not considered related to the trial treatment.

- Results in death
- Life-threatening (i.e. at the time of the event)*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is considered medically significant by the Investigator***

*Life threatening means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.

**Requires in-patient hospitalisation should be defined as a hospital admission required for treatment of an AE.

***Considered medically significant by the Investigator are events that may not result in death, are not life threatening, or do not require hospitalisation, but may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

9.1.4 Serious Adverse Reaction (SAR)

A serious adverse reaction (SAR) is a SAE that may be related to trial treatment. The assessment of "relatedness" is primarily the responsibility of the Principal Investigator (PI) at site or agreed doctor designee. SAEs will be considered related if the SAE is documented as possibly, probably or definitely related to protocol treatment. The assessment of relatedness is made using the following:

Relationship	Description
Unrelated	There is no evidence of any causal relationship.
Possible	There is some evidence to suggest a causal relationship (e, g. the event occurs within a reasonable time after administration of the trial medication). However the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors in unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

9.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any suspected SAR that is unexpected. Unexpected is any reaction that is not a known reaction listed in the appropriate section of the current regulatory approved Investigator Brochure (IB) or Summary of Product Characteristics (SmPC), which is acting as the reference safety information (RSI) for the trial treatments. Please note the version of the RSI that has regulatory approval may not be the most up-to-date version of the IB or SmPC that has been provided to Investigators for advice on the clinical management of their trial patients.

9.1.6 Adverse Event of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be

serious or non-serious. Serious AESIs which meet the criteria of SAEs should be reported as such. Refer to the drug-specific appendix for further guidance.

9.2 Detecting, Recording and Reporting of Adverse Events

9.2.1.1 Detection of Adverse Events

Participants will be asked at each trial visit about the occurrence of AEs since their last visit.

AEs will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and the trial protocol.

AEs must be recorded as they are reported, whether spontaneously volunteered or in response to questioning about well being at trial visits. The questioning about AEs will cover the current visit as well as the period of time between the previous and the current visit. All AEs must be documented in the patient's medical records whether they are required to be recorded in the eCRF or not.

9.2.1.2 Recording of Adverse Events

Full details of AEs including the nature of the event, start and stop dates, severity (CTCAE grade), seriousness and causality (relationship to trial drug) and outcome will be recorded in the patient's medical records. AEs occurring between signing pre-screening consent and drug subgroup consent should only be recorded on the eCRF if they are a result of a study related procedure. All AEs occurring after drug subgroup consent prior to the start of study IMP require to be recorded on the eCRF.

All AEs must be followed until resolution, or for the time period specified in the drug-specific appendix, whichever comes first, or until toxicity has resolved to baseline or ≤ grade 1, or until the toxicity is considered to be irreversible. Perceived lack of efficacy is not an AE.

An exacerbation of a pre-existing condition is an AE.

9.2.2 Assessment of Adverse Events

All AEs and toxicities must be coded and graded according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. These criteria can be accessed via the National Cancer Institute Website, please see Appendix III for further details.

AEs must be assessed for seriousness (the SAE category/definition that has been met), causality (the relationship to the study drug) and severity. This assessment is the responsibility of the PI (or doctor designee).

For trial treatments that are double blind, AEs should be assessed as though the patient was taking the trial drug.

The assessment of expectedness for regulatory reporting will be undertaken by the CRUK Glasgow CTU and CI. For the purpose of safety reporting, more severe forms of adverse reactions indicated as non-serious will always be considered unexpected, and any adverse reactions that are immediately life-threatening or result in death.

9.2.3 Reporting of a Serious Adverse Event

Serious adverse Events (SAEs) must be reported to the Pharmacovigilance Office, CRUK Glasgow CTU immediately and under no circumstances should this exceed 24 hours following awareness of the event by the Investigator or site staff. A current version of the ATLANTIS SAE reporting form must be completed and submitted to:

Pharmacovigilance Office, CRUK Glasgow CTU
Email: mvls-ctu-pv@glasgow.ac.uk
Tel no: +44 (0) 141 211 3567/0352/3968/0203

For guidance on submitting and completing the initial and follow up SAE report forms please refer to the SAE Completion Guidelines, which will be provided by the Pharmacovigilance Office, CRUK Glasgow CTU.

The CI will receive notification, by email, of all SAEs received.

SAEs must also, if required, be reported locally by the PI at each site in accordance with the local practice at their site (i.e. R&D Office).

A follow-up report must be completed and submitted when the SAE resolves, is unlikely to change, or as soon as additional information becomes available. If the SAE is a suspected SUSAR then follow up information must be provided as quickly as possible and in the timeframe

requested by the CRUK Glasgow CTU and CI. All follow-up information is required to be reported promptly and follow up reports must be submitted until all AEs listed on the initial SAE report resolve or it is confirmed will never resolve. A follow up report should also be submitted if additional AEs occur or new information becomes available about a previously reported AE.

SAEs are required to be reported from pre-screening consent until drug subgroup consent only if they are a result of a study related procedure. All SAEs occurring after drug subgroup consent up to 30 days after last administration of trial treatment are required to be reported unless specified differently in the drug-specific appendix. Any SAE that occurs after the minimum reporting period defined in the relevant appendix, and up to the end of the trial, is also required to be reported if the Investigator thinks that the SAE is related to protocol treatment (is a SAR).

SAEs that do not require to be reported include any planned hospitalisation for reasons unrelated to trial treatment.

For any questions relating to SAE reporting, please contact the Pharmacovigilance team,
Email: mvls-ctu-pv@glasgow.ac.uk
Telephone: 0141 211 3567/0352/3968/0203

Contact details are also provided at the front of the protocol and in the SAE Completion Guidelines.

9.2.4 Identifying SUSARs

The assessment of expectedness for SAEs and regulatory reporting will be undertaken by the CRUK Glasgow CTU and CI. This will be based on the section(s) of the RSI for the novel agents agreed with the manufacturers that have regulatory approval to act as the RSI, in effect at the time the SAE occurs.

When deciding if an event is unexpected consideration will be made by the CI as to whether the event adds significant information of the specificity, increase of occurrence or severity of a known, serious adverse reaction that is already recognised and documented in the RSI. Please note that for unlicensed IMPs any SAR that is fatal or immediately life-threatening will automatically be reported as a SUSAR whether recorded in the RSI as an AE with fatal outcome, or not.

9.2.5 Reporting of a SUSAR

CRUK Glasgow CTU on behalf of the Co-Sponsors is responsible for the expedited reporting of all SUSARs to the required Regulatory Authorities, Research Ethics Committee (REC), PI at trial sites and the trial Sponsor(s) as well as the pharmaceutical company (as per any agreements).

- Fatal or life threatening SUSARs will be reported within 7 days of the CRUK Glasgow CTU receiving the first notification of the unexpected event. Any additional information will be reported within eight days of submitting the initial report
- All other SUSARs will be reported within 15 days of the CRUK Glasgow CTU receiving the first notification of the unexpected reaction.
- SUSARs which initially are considered to be non-fatal or non-life threatening but which turn out to be fatal or life-threatening, will be reported as soon as possible and no later than 7 days after the CRUK Glasgow CTU becoming aware of the reaction being fatal or life-threatening. If this report is incomplete a completed follow-up report will be submitted within an additional 8 days.
- SUSARs which initially are considered to be non-fatal or non-life threatening but which turn out to be fatal or life-threatening, if the initial report has yet to be submitted, will have a combined report submitted.

If the assessment of causality provided by the investigator differs from that of the CI (assessment is made on behalf of the Sponsor), the opinion of both the Investigator and CI will be provided in the SUSAR report.

9.2.6 Processes for Expedited Reports of SUSARs for Blinded Trials

SUSAR reports must be submitted to the Regulatory Authority, REC and Sponsor unblinded. If, when unblinded, it is found that a patient is receiving IMP, then a SUSAR report will be submitted to the Regulatory Authority and then circulated to the REC, Sponsor and pharmaceutical company, if applicable. As the eSUSAR generated SUSAR report identifies the patient's treatment allocation, a report of the SAR will be generated from the trial database and submitted by email to the trial sites as the report of an event identified by the CI as a SUSAR. The CI and Project Manager (PM) will be included in this correspondence with the sites.

If, when unblinded, it is found that the patient is receiving placebo, then a doctor designee, agreed by the Sponsor, will be contacted. The designee will be provided with details of the SAR and asked to confirm if the placebo could have caused the event.

If the placebo is considered not to be implicated in the event, then the SAR will not be reported as a SUSAR to the Regulatory Authority, or the REC. The Sponsor will be informed by email that a SUSAR has been identified by the CI, but the patient is receiving placebo and the CI designee has confirmed the placebo could not have caused the event. To maintain the trial blind for the CI, reporting Investigator and site staff, a blinded report will be generated from the SAE report data entered into the database and submitted to the trial sites by email following the usual procedure for SUSARs by including the CI and trial PM in the correspondence. The Sponsor will also be sent this report.

If the placebo is thought to have caused the event (as a result for example of a manufacturing error), then the SAR will be reported as a SUSAR using eSUSAR and circulated to the REC, Sponsor and pharmaceutical Company (if applicable). Again, to maintain the trial blind, a report generated from the SAE report data entered into the electronic reporting systems will be circulated to the participating sites by email following the usual procedure of including the CI and trial PM.

9.2.7 Other Unexpected Events Requiring Regulatory Reporting

In addition to SUSARs there may be other events that are relevant in terms of the risk-benefit balance. In addition to SAEs, SARs and SUSARs, all unexpected events that might materially influence the risk-benefit assessment of the IMP(s) or that would lead to changes in the administration of an IMP or in the overall conduct of a trial will also be reported to the Regulatory Authorities. This includes events which:

- Could be associated with trial procedures which could modify the conduct of the trial
- May be an increase in the rate of occurrence of an expected SAR which may be clinically important
- Potentially could be a significant hazard to the patient population such as a lack of efficacy of the IMP (s)
- Are major safety findings from a newly completed studies (including animal studies)
- Would include the temporary halt of a trial for safety reasons in a trial with the same IMP also conduct by the Sponsor

Other unexpected events must be reported to the required Regulatory Authority without delay, by the appropriate method (as an urgent safety measure, substantial amendment or early termination of the trial). Regulatory Authority, Ethics Committees and the Sponsor will be informed of any safety issues that might materially alter the current benefit-risk assessment of the IMP(s) while not falling into the actions for SUSARs noted above.

9.3 Pregnancy

Pregnancy occurring in a clinical trial participant, or the partner of a participant, while not considered an AE or a SAE, requires monitoring and follow-up.

The Investigator must collect pregnancy information for female trial subjects or female partners of male trial subjects. This includes subjects who become pregnant while participating in a clinical trial of an investigational medicinal product (IMP) or during a stage where the foetus could have been exposed to the IMP.

Male patients should refrain from fathering a child or donating sperm during the trial and for the stated time period in the drug-specific appendix following the last dose of trial treatment.

Patients of childbearing potential and their partners, who are sexually active, must agree to the use of 2 forms of contraception, one of which should be highly effective (defined as achieving a failure rate of less than 1% per year) and one acceptable (cannot be defined as highly effective as it results in a failure rate of more than 1% per year) barrier method, such as the male condom (see examples below). They must continue this throughout their participation in the trial and for the stated time period in the drug-specific appendix, after last dose of trial drug. The necessity of adherence to the contraception requirements should be part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate highly effective contraception.

One form of highly effective contraception should be used, such as:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation :
    - Oral
    - Intravaginal
    - Transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner – provided the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Sexual abstinence – defined as refraining for heterosexual intercourse during the entire period of risk associated with the study treatment (confirm period per trial). This must be true abstinence in line with the preferred lifestyle of the participant.

One form of acceptable barrier method contraception should also be used, such as:

- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

Contraceptives should be effective before Day 1 of drug administration, throughout the trial and for the time specified in the drug-specific appendix, after completing the trial. It should be explained to male patients that if his partner is pregnant or breast-feeding when he enters the trial, the patient should use barrier method contraception to prevent the unborn baby or the baby being exposed to the trial drug.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with IMP and occurring up to the time specified in the drug-specific appendix after the last IMP administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient and the baby should continue until the conclusion of the pregnancy, if the patient or patient's partner has consented to this.

However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed:

- Any pregnancy occurring in a patient or a patient's partner during treatment with IMP or occurring within the time specified in the drug-specific appendix for the treatment must be reported to the CRUK Glasgow CTU Pharmacovigilance Department initially by completing the pregnancy notification eCRF and also within 24 hours of the site staff becoming aware

of it by submitting a completed Pregnancy Notification Form (PNF) via email mvls-ctu-pv@glasgow.ac.uk. It is the Investigator's responsibility to obtain approval for follow-up from the patient or patient's partner. The Pharmacovigilance Department of the CRUK Glasgow CTU will follow-up all pregnancies until the pregnancy outcome via the Investigator, using the PNF.

- The PI must update the PNF with the outcome of the delivery or if there is a change in the subject's condition such as miscarriage or planned termination. The updated PNF must be sent (email mvls-ctu-pv@glasgow.ac.uk) to the Pharmacovigilance Department as soon as any new the information becomes available.
- Any pregnancies that result in a congenital anomaly or birth defect will require to be reported as a SAE. The Pharmacovigilance Department will advise on reporting pregnancies as SAEs.

SAEs that are the result of a birth defect will be reported as SUSARs if the CI and Sponsor consider the birth defect to be unexpected.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR FURTHER GUIDANCE ON PREGNANCY *****

9.3.1 Development Safety Update Reports

Development Safety Update Reports (DSURs) will be prepared by the CI and CRUK Glasgow CTU and submitted on behalf of the Sponsor for the trial. This report will include data for each of the subgroups. An unblinded version of the DSUR will be submitted to the Regulatory Authority, REC, trial Sponsor(s) and the relevant subgroup section of the DSUR to pharmaceutical company within 60 days of the anniversary of obtaining the UK Clinical Trial Authorisation. DSURs will continue to be submitted until the End of Trial notification has been submitted.

9.3.2 Non Investigational Medicinal Products (NIMPs)

Non Investigational Medicinal Products (NIMPs) are "products which are not IMPs" and are referred to in Art. 2(d) of Directive 2001/20/EC and may be supplied to patients participating in a trial and used in accordance with the protocol.

Any nIMPs will be listed in the drug-specific appendix.

9.3.3 COVID-19 Vaccination/Treatment and Safety Reporting

Where a deployed COVID-19 vaccine or treatment is suspected to be involved in the onset of a reported event it should be recorded as a concomitant medication. A causal relationship between the vaccine/treatment and the event, including potential drug interactions should be assigned by the reporting investigator.

If a reported event is suspected to be due to a deployed COVID-19 vaccine or COVID-19 medicine alone reporting investigators should ensure that standard Yellow Card reporting procedures are followed.

9.3.4 Reference Safety Information

The RSI for each subgroup will be specified in the drug-specific appendix. This will usually be the agreed section of the IB provided by the pharmaceutical company for the novel trial drug which will act as the RSI for the trial. The pharmaceutical company providing the trial drug is responsible for supplying the Sponsor with updated IBs with UK Regulatory approval within the number of days specified in the relevant pharmaceutical agreement. However, only the IB with current regulatory approval for use in the trial DSUR reporting period (the RSI must remain unchanged within the DSUR reporting period) will be used to assess the expectedness of SAE reports to identify SUSARs.

If RSI is contained within an SmPC, the contents of Section 4.8 Undesirable Effects in the SmPC identified by the Sponsors for the trial will act as the RSI for the trial drug or IMP. The Sponsors are responsible for identifying and informing the CRUK Glasgow CTU of updates to the reference SmPC. Only the SmPC with current regulatory approval for the trial within the DSUR reporting period (the RSI will remain unchanged within the DSUR reporting period) will be used to assess the expectedness of SAE reports to identify SUSARs. The RSI will continue to be maintained until the last patient has attended for their last follow-up visit.

9.3.5 Changes to the RSI or Risk-Benefit Assessment

If changes to sections of the relevant documents (eg. IB or SmPC) that constitute the RSI include the addition of new reactions now considered expected, an update that impacts on patient safety

or if the risk-benefit assessment or clinical management of trial participants is affected by an update to the RSI, then the RSI will not change for the duration of the DSUR reporting period however the updated IB/SmPC will:

- Be submitted to trial sites for their information .
- A front sheet document for use when the risk benefit or clinical management has changed will accompany the reference documents and provide guidance on the current RSI and IB/SmPC to be referred to for the clinical management of trial patients.
- If patient safety/or the risk-benefit assessment has changed and/or new expected reactions have been added, then approval of the updated RSI will be made by submitting a substantial amendment to the Regulatory Authority and REC.

Changes that impact on patient safety or alter the risk-benefit assessment may require changes to the trial documentation such as the patient information sheet. The CI on behalf of the Sponsor will identify any such required changes. The CRUK Glasgow CTU will seek approval of the changes, as required by the clinical trial regulations.

9.3.6 Changes that do not alter the Risk-Benefit or Clinical Management

If changes to the RSI are minor and do not include new expected reactions, do not impact on patient safety or alter the risk-benefit assessment or the clinical management of the trial participants, then the RSI will not change for the DSUR reporting period and:

- Investigators will not receive/be informed of the updated IB/SmPC until the end of the DSUR reporting period and this decision will be made by the Sponsor.
- It may be decided to not update the RSI in the new DSUR reporting period if the changes are very minor. However if the updated RSI is to be implemented in the new DSUR reporting period then approval of the updated RSI will be made by informing the Regulatory Authority in the trial DSUR of the intention to implement the updated RSI after the current DSUR reporting period ends. The updated RSI will be attached to the DSUR. If new expected reactions have been added to the RSI or events have downgraded to expected, then the updated RSI must receive approval by substantial amendment before it will be implemented (see 9.3.3).
- If the RSI is updated it will be sent to the trial sites with an updated front sheet documenting the change in RSI. This will be circulated before or at the start of the new DSUR reporting period.

10 EFFICACY EVALUATION

10.1 General

Assessment and reporting of tumour response will be done in accordance with the model established by the Response Evaluation Criteria in Solid Tumours (RECIST v.1.1) group. All patients included in the treatment phase of the trial must be assessed for response to treatment, even if there are major protocol deviations or if they are ineligible. Each patient will be assigned one of the following categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or non-evaluable including early death from malignant disease, early death from toxicity, early death because of other cause, not assessable or insufficient data.

All efficacy analysis will be performed on the intent to treat population. To ensure comparability, the same method of assessment must be used throughout the trial for each marker lesion.

10.2 Disease measurability (RECIST 1.1 criteria)

See appendix IV. For the purposes of this trial, the appearance of new non-muscle invasive cancer in the bladder will not constitute a new lesion and will not, therefore, constitute disease progression.

10.3 Timing of Measurements

10.3.1 Screening / Baseline evaluation

Radiological evaluation will take place within 4 weeks before randomisation to trial drug subgroup.

10.4 Response Criteria

10.4.1 Evaluation of Target-Measurable Lesions

The measurement of the longest diameter only for all target-measurable lesions is to be used and assessed at baseline, after 12 week intervals (up to 36 weeks). Table 10.1 summarizes the criteria to be used in evaluating the response of target-measurable lesions:

Best Response	**Change in the sum of longest diameters (LD) of target-measurable lesions**
Complete Response (CR)	Disappearance of all target lesions determined by 2 observations not less than 4 weeks apart

Partial Response (PR)	At least a **30% decrease** in the sum of LD of target lesions determined by 2 observations not less than 4 weeks apart and taking as **reference the baseline sum LD** (the scheduled tumour evaluation is 9 weeks apart). It is not necessary for all lesions to have regressed to qualify for partial response, but no lesions must have progressed and not one additional new lesion should appear.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD determined by 2 observations not less than 4 weeks apart.
Progression (PD)	At least **a 20% increase in the sum of LD** of target lesions taking as **reference the smallest sum LD** recorded since the treatment started or the **appearance of one or more new lesions.** Assignment to the progression category is done after 6 weeks from trial entry. When the progression is observed before 6 weeks after entry in the trial, the patient will be considered as an "early progression".

Table 10.1. Evaluation of Target-Measurable Lesions

10.4.2 Evaluation of Non Target-Non Measurable Lesions

Definitions of the criteria used to determine the objective response for non-target lesions are as follows and summarized in Table 10.2.

Best Response	**Change in the sum of longest diameters (LD) of target-measurable lesions**
Complete Response (CR)	Disappearance of all non-target non-measurable lesions determined by 2 observations not less than 4 weeks apart
Incomplete Response/ Stable Disease	Persistence of one or more non-target non-measurable lesion
Progression (PD)	**Appearance of one or more new lesions.** Unequivocal progression of existing non-target non-measurable lesions. (New or recurrent non-muscle invasive disease will count as new lesion)

Table 10.2. Evaluation of Non-Target Non-Measurable Lesions

10.4.2.1 Definition of progression free survival

In the ATLANTIS trial, progression-free survival (PFS) will be the time from randomisation until progression (as defined by sections 10.4.1 and 10.4.2 above) or death, whichever occurs first. Where a patient commences further systemic anti-cancer therapy before progression has occurred, the patient will be considered to have progressed on the day they start that treatment for disease progression.

10.4.3 Assessment of Best Overall Response

Best overall response is the best response recorded from the start of treatment until disease progression taking as reference for progressive disease the smallest measurements recorded since the treatment started. Complete and partial responses have to be confirmed by two evaluations of the disease, taken at least 4 weeks apart.

The determination of the overall response should be done according to the following Table 10.3:

Target-Measurable Lesions	Non Target-Non Measurable Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete Response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 10.3. Determination of the overall response

11 STATISTICS AND DATA ANALYSIS

11.1 Trial Design and Sample Size

Within each ATLANTIS subgroup component the design is based around a randomised phase II screening design to detect a certain level of improvement in median PFS with the novel drug compared to placebo/observation with 90% power, at the 20% 1-sided level of statistical significance (or equivalently with 80% power at the 10% level of statistical significance).

At the end of the trial, if the observed PFS difference in favour of the novel agent is statistically significant at 10% this will be a clear signal that a subsequent phase III trial is warranted. A result that is statistically significant at the 20% level (but not 10%) will require supportive data in terms of improvement in the reduction of size of measurable disease (LAMB suggest 85% of patients will have measurable disease) before a subsequent phase III would be considered. This decision making process follows a 3- outcome type design (Shengyan Hong and Yanping Wang A three-outcome design for randomized comparative phase II clinical Statist. Med. 2007; 26:3525–3534).

Details of the improvement in median PFS, recruitment rates and overall sample size required in each of the current ATLANTIS drug subgroups can be found in the relevant appendix.

11.2 Analysis Plan

The analysis plans for all patient subgroups are identical and are summarised below:-

All analyses will be conducted on an intention-to-treat basis. PFS will be compared between the trial arms in 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.

The comparison of OS will be as above.

- At the end of the trial if the observed PFS difference in favour of the experimental arm is statistically significant at 10% this will be a clear signal that a subsequent phase III study is warranted.
- A result that is statistically significant at the 20% level (but not 10%) will require supportive data in terms of a statistically significant improvement in the maximum percentage decrease in measurable disease (at the 10% level) to indicate a phase III trial is warranted. A Mann-Whitney U-test will be used for this comparison.

- The overall survival and PFS will be illustrated using Kaplan-Meier plots.
- Response rates will be compared between the trial arms in the context of a logistic model incorporating the baseline minimisation factors. The p-value for the observed odds ratio will be determined from this model.
- The worst toxicity grades experienced during chemotherapy will be compared using the Mann-Whitney U test.

11.3 Interim Analysis

The study data will be reviewed approximately annually by an Independent Data Monitoring Committee (IDMC). In all patient subgroups there is a non-binding test for futility after half the PFS events have occurred based on a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule. The IDMC will also review toxicity, treatment delivery and compliance data. The IDMC recommendation will take into account all available data as well as the futility comparison of PFS.

12 TRIAL CLOSURE/DEFINITION OF END OF TRIAL

The **trial** will end when the Trial Management Group agrees that one or more of the following situations apply:

- The trial has completed as planned, all patients have been followed up as per protocol and there are no new subgroups planned, in development or there is no further potential to seek additional subgroups to investigate.
- There is insufficient funding to support further recruitment to the trial as a whole and no reasonable prospect of additional support being obtained.
- New information makes it inappropriate to continue to randomise to any of the current subgroups and this also makes it inappropriate to remain open to pursue new subgroups for investigation.
- Recruitment is so poor that completion of the trial as a whole cannot reasonably be anticipated.

and, for all subgroups within the umbrella protocol:

- All outstanding data has been returned from all sites, all required data queries have been resolved and the database is finalised to allow analysis to take place to answer all protocol endpoints for all subgroups. This will be considered the date of last data capture and the end of trial will be the date this has been met.

At this point the End of Trial Declaration will be submitted.

Individual trial subgroups within the umbrella protocol will close when one of more of the following situations apply:

- The subgroup has completed as planned, and all patients have completed follow up as per protocol, and no further follow-up data will be collected
- The independent Data Monitoring Committee has advised discontinuation of the subgroup e.g. because of safety concerns, or a statistically significant difference in clinical outcomes is evident between the treatment subgroups
- There is insufficient funding to support further recruitment to the subgroup and no reasonable prospect of additional support being obtained
- New information makes it inappropriate to continue to randomise to the study subgroup
- Recruitment is so poor that completion of the subgroup cannot reasonably be anticipated

And, for the individual arm:

- All outstanding data has been returned from sites, all required data queries have been resolved and the database is finalised to allow analysis to take place to answer all protocol endpoints for the subgroup.

The closure of individual trial subgroups has no impact on the end of trial being met, and as such the End of Trial Declaration being submitted, unless the aforementioned criteria detailed above has been met to necessitate the trial end.

12.1 End of Trial Notification

End of trial notification will be submitted to the competent authority and REC within 90 days using the 'Declaration of the End of a Clinical Trial' form that can be found on the EudraCT website. However, if the trial is terminated either (1) before the date for the conclusion of the trial specified in the protocol for that trial or (2) before the number of events required by the trial has occurred,

the competent authority and REC will be notified in writing of the termination of the trial within 15 days of the date of termination with a clear explanation of reasons and details of follow-up measures, if any, taken for safety reasons.

12.2 Clinical Trial Summary Report

The clinical trial summary report should be submitted to the competent authority within one year of submitting the end of trial notification. The content and format of the report should follow guidelines published on the MHRA website. The CI in association with CRUK Glasgow CTU is responsible for compiling and submitting the final report to both Sponsor(s) and MHRA.

13 DATA HANDLING

13.1 eCRFs

The clinical trial data should be recorded on the ATLANTIS electronic case report forms (eCRFs). The eCRFs for this trial will be completed using the electronic remote data capture (eRDC) system, MACRO®. Prior to recruitment beginning at each site, training will be provided on the MACRO® system.

It is the responsibility of the Principal Investigator to ensure eCRFs are completed in a timeous manner and to review and approve all data captured on the eCRF.

Please ensure that all data submitted on eCRFs is verifiable in the source documentation or that any discrepancies are recorded and explained.

Other essential documents, including source data, consent forms, and regulatory documentation, will be archived by, or for the Investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required.

13.2 Data Return and Escalation Processes

CRUK Glasgow CTU will regularly chase outstanding data from participating sites. Routine requests for outstanding data and outstanding data queries will be performed quarterly or more regularly if required for a specific trial.

Sites will be routinely requested to return outstanding data and data queries within 6 weeks of receiving the queries or the eCRF being due for completion.

Trigger reports will be run quarterly at the same point as the routine requests for data. If any site has 20% of forms overdue for more than 3 months (at least 10 forms meeting this criteria) or any forms greater than 6 months overdue the site will be contacted. A log will be kept of any sites meeting a trigger point. If a site consistently meets a trigger point an escalation process will be begin.

Data Escalation Process

Step 1: E-mail letter to site main contact and copy in site PI
Step 2: E-mail letter direct to site PI and copy in site main contact
Step 3: E-mail letter to Network Coordinator and copy in site PI and main contact
Step 4: Discuss suspension of recruitment at site until data issues resolved

13.3 Record Retention and archiving

Archiving of the trial essential documents should be performed by both the participating trial site and Sponsor/CRUK Glasgow CTU.

Participating sites are responsible for archiving their trial related documentation and should follow the requirements of their R&D Office in conjunction with advice from the CRUK Glasgow CTU and Sponsor regarding the duration of document retention. Sites should not archive their trial documentation until they have been instructed by the CRUK Glasgow CTU or Sponsor that they are able to do so. Where possible, at the time of archiving, sites will be notified of the archiving retention period. If this is not confirmed at the time of archiving, sites should not destroy archived documentation until authorisation is given from the Sponsor.

The Sponsor and CRUK Glasgow CTU will be responsible for archiving the Trial Master File (TMF) and all other essential trial documentation that is not held at participating trial sites as per their applicable SOPs.

In the event that a patient's care is transferred to another hospital a Patient Transfer Form must be completed and returned to CRUK Glasgow CTU. The original randomising site will be

recognised with the recruitment of the patient. The randomising site will continue to be responsible for returning all outstanding trial documents that are due until the date of transfer and any documents required after the date of transfer will be the responsibility of the site the patient was transferred to.

14 TRIAL MANAGEMENT

14.1 Trial Start Up

Sites wishing to participate in the trial should contact CRUK Glasgow CTU. A PI must lead the trial at each site and they will be responsible for providing CRUK Glasgow CTU with all core documentation. Protocol training will be given to sites via initiation slides that will be provided to sites prior to the trial opening at that site. Once all the documentation is received at CRUK Glasgow CTU an initiation call will be performed and after this, the site will be contacted by email or fax when they are activated and are able to recruit patients to the trial.

14.2 Core Documents

The core documents may include and are not limited to:

- Signed Clinical Trial Agreement
- Local R&D approval or Confirmation of Capability and Capacity as per HRA Approval process (for English sites)
- Delegation and Study Specific Training Log
- CV and GCP (for PI and Lead Pharmacist)
- Lab accreditation certificates and normal ranges (biochemistry and haematology)
- PIS/CF, GP Letter and Patient Results Letter on local headed paper
- Initiation acknowledgements
- Signed Pharmacy Assessment Form
- Site Initiation/Accreditation Checklist

14.3 Management of protocol deviations and violations

14.3.1 Deviations

Organisations must notify the Sponsor (via CRUK Glasgow CTU) of all deviations from the protocol or GCP immediately. The Sponsor requires a report on the incident(s) and a form will be provided

during site initiation. If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the CRUK Glasgow CTU trial team and Co-Sponsors can be contacted immediately to discuss. The Sponsor will assess all incidents against the definition of a "serious breach".

14.3.2 Serious Breach

Events that match the criteria of a "serious breach" will be reported to the REC within 7 days of the matter coming to the attention of the Sponsor.

National Research Ethics Service SOP for Research Ethics Committees (version 6.1, January 2015) defines a "serious breach" as "a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards of conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of trial subjects or the scientific value of the research".

The report should include details of when the breach occurred, the location, who was involved, the outcome and any information given to the participants. The REC should also be informed of any further corrective or preventative action the Sponsor plans to take.

Events that match the criteria of a serious breach of GCP/study protocol, as defined in regulation 29A of UK statutory instrument 2006/1928, will be reported to the MHRA within 7 days of the Sponsor becoming aware of the serious breach. Reports will be submitted using the report template published by the MHRA. The Sponsor will respond to any queries raised by an MHRA representative in light of a serious breach report submission.

Investigators should report potential serious breaches to the CRUK Glasgow CTU and/or Sponsor as soon as practically possible.

14.4 Trial Management Group (TMG)

The trial will be coordinated from CRUK Glasgow CTU by the TMG. The TMG normally includes those individuals responsible for the day-to-day management of the trial. Members of the TMG include the CI, Co-Investigators, Project Manager, Trial Statistician, Clinical Trial Monitor, Pharmacovigilance Team and Sponsor Pharmacist. The role of the group is to monitor all aspects

of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

14.5 Trial Steering Committee (TSC)

The CRUK Glasgow CTU Umbrella Trial Steering Committee (UTSC) will act as the Trial Steering Committee for this trial. The role of the UTSC is to provide overall supervision of the trial to ensure it is being conducted in accordance with the principles of GCP, to review progress of the trial and to provide advice to the CI. The UTSC has members who are independent of the trial. Decisions about continuation or termination of the trial are the responsibility of the UTSC.

14.6 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to review the accruing trial data and to assess whether they are any safety or efficacy issues that should be brought to participants' attention or any reasons for the trial not to continue. The IDMC will be independent of the investigators and will be the only body that may have access to unblinded data during the course of the trial. It will make recommendations to the TSC.

15 REGULATORY ISSUES

15.1 Clinical Trials Authorisation (CTA)

On behalf of the trial Sponsor, CRUK Glasgow CTU will apply to the MHRA for a clinical trials authorisation (CTA) to conduct the trial and will also be responsible for the maintenance of the CTA.

15.2 Ethics Approval

Ethics favourable opinion will be sought for the trial from a REC prior to commencement of the trial. Further to that approval, each participating site will be responsible for obtaining their own local approval by submitting an SSI to their appropriate R&D department for management approval (for devolved nations), or by obtaining Confirmation of Capability and Capacity via the HRA approvals process (English sites).

Participating sites will not be activated to recruitment until management approval has been obtained, and a signed Clinical Trial Agreement between the local R&D office and the trial Sponsor has been executed.

The trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000], Washington (2002), Tokyo (2004), Seoul (2008) amendments.

15.3 Consent

Consent to enter the trial must be sought from each participant only after full explanation has been given, an information sheet offered and time allowed for consideration. Signed participant consent must be obtained, the consent forms should also be signed by the person carrying out the consent procedure at site, who must be detailed on the Delegation and Study Specific Training Log as having authorisation. The PI is responsible for ensuring if the taking of consent is delegated to a designee the designee is suitably qualified by training or experience to take informed consent.

The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the best interests of the participant, but the reasons for doing so must be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

An original completed consent form must be retained at each site in the appropriate section of the Investigator Site File, and a photocopy placed in the patient's medical records. All patients must be given an original of the signed patient information sheet and consent form for their records. Consent forms must be retained on site and not submitted to the trials office.

In the event that new patient information sheets/consent forms are produced throughout the duration of the trial, it maybe that patients already participating in the trial should be re-consented to the updated version of the patient information sheet. However, if the PI decides that this is not in the best interests of the patient re-consent is not required. Decisions to not re-consent patients must be documented in the patient's medical records.

15.4 Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CRUK Glasgow CTU. The CRUK Glasgow CTU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- Consent from participants to record personal details including patient initials, date of birth, CHI/NHS number, hospital number, GP name and address.
- Appropriate storage, restricted access and disposal arrangements for patient's personal and clinical details
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Data collection forms that are transferred to or from the CRUK Glasgow CTU will be coded with a trial number and will include two patient identifiers, usually the patient's initials and date of birth.
- Where central monitoring of source documents by CRUK Glasgow CTU (or copies of source documents) are required (such as scans or local blood results), the patient's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CRUK Glasgow CTU.
- If a participant withdraws consent from further trial treatment and / or further collection of data their samples will remain on file and will be included in the final trial analysis unless they specifically withdraw consent for this.

15.5 Liability, Indemnity and Insurance

The Hospital Trust/Health Board at each participating site is responsible for the following:

1. Acts and omissions of its own staff and others engaged by it, including the Clinical Trials Unit and PI;
2. Ensuring the appropriate insurance administered by the National Health Service Litigation Authority is in place;

3. Ensuring any non-NHS employees involved in the clinical trial have Honorary Contracts with the Trust/Board to cover access to patients and liability arrangements.

These responsibilities are outlined and agreed within the Clinical Trial Agreement.

No special insurance is in place for patients in this trial other than standard NHS liability insurance providing indemnity against clinical negligence. This does not provide cover for non-negligence e.g. harm caused by an unexpected side effect of participating in a trial. The Sponsors have responsibility for ensuring that financial cover for damages or compensation arising from no fault harm is available to patients, where applicable. The Co-Sponsor, the University of Glasgow, maintains clinical trials insurance. Cover for this clinical trial has been agreed under the current policy.

15.6 Sponsor(s)

NHS Greater Glasgow & Clyde and the University of Glasgow will act as Co-Sponsors for this trial. Delegated responsibilities will be assigned to the CRUK Glasgow CTU and NHS Trusts/Boards taking part in this trial. Details of responsibilities will be outlined in the Clinical Trial Agreement that should be signed prior to site initiation.

15.7 Funding

The trial will be partly funded by CRUK Glasgow Clinical Trials Awards and Advisory Committee.

Please refer to the Clinical Trial Agreement for full information on any per patient payments or investigator payments due to site.

*****PLEASE REFER TO DRUG-SPECIFIC APPENDIX FOR DRUG SPECIFIC FUNDING *****

15.8 Protocol Amendments

Any change to the trial protocol will require an amendment. Any proposed non administrative protocol amendments will be initiated by the CI following discussion with the TSC and any required amendment forms will be submitted to the regulatory authority, REC and Sponsor(s). The CI and the TSC will liaise with trial Sponsor(s) to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor(s)

representative. Before the amended protocol can be implemented favourable approval must be sought from the original reviewing REC, trial Sponsor(s), MHRA (if applicable) and participating site R&D offices.

16 QUALITY ASSURANCE

16.1 Audits and Inspections

Trial Investigators must permit trial related monitoring, audits, REC review and regulatory inspections as required, by providing direct access to source data, CRFs and other documents (patient's medical records, trial site file, and other pertinent data). The trial may be subject to inspection and audit by NHS Greater Glasgow and Clyde under their remit as Co-Sponsor, the CRUK Glasgow CTU and other regulatory bodies, i.e. the MHRA, to ensure adherence to GCP. If an inspection is scheduled at any participating site, the site must notify the CRUK Glasgow CTU at the earliest opportunity.

16.2 Allocation of Trial Responsibilities

The Co-Sponsors of this clinical trial are NHS Greater Glasgow & Clyde and the University of Glasgow. A Co-Sponsor agreement will be in place to outline the responsibilities of each Co-Sponsor.

A Clinical Trial Agreement will be put in place between NHS Greater Glasgow & Clyde and each of the participating sites. This agreement outlines the responsibilities of each party's responsibilities in the running of the trial as well as the Chief Investigator (CI), the CRUK Glasgow CTU and the Principal Investigator (PI) at the Participating Site.

16.3 Co-Sponsor Responsibilities (NHS GG&C/University of Glasgow)

The Sponsor's responsibilities will be for Authorisation and REC opinion, GCP and Conduct, and Pharmacovigilance. The majority of the Sponsor's responsibilities have been delegated to the Chief Investigator (CI) who performs these via the CRUK Glasgow CTU as the co-ordinating centre for the trial. As such, the main role of the Sponsor(s) is to ensure that the CI and CRUK Glasgow CTU fulfil their responsibilities as outlined in the Clinical Trial Agreement and to ensure that any identified "risks" either have controls or action points put in place.

16.4 Chief Investigator (CI)

The CI has delegated the majority of his/her responsibilities to the CRUK Glasgow CTU. The CI is directly responsible for ensuring the protocol and any amendments are in place, for review of SAEs and determination if SAEs meet the criteria for a SUSAR. The CI is also responsible for providing advice and recommendations on medical issues that arise involving the management of the patients on the trial. From the perspective of the Co-Sponsor and for regulatory/ethics purposes, the CI for the trial will be Professor Rob Jones.

16.5 CRUK Glasgow Clinical Trials Unit (CTU)

The CRUK Glasgow CTU is responsible for the overall management of the clinical trial. This includes all regulatory submissions (REC, R&D and CTA) and any amendments, all administration relating to the submissions and any amendments, circulation of all correspondence to participating sites, data management, monitoring of data quality and safety, ongoing communication with participating sites, management of SAE/SUSAR reporting, and where applicable the management of any financial arrangements.

16.6 Participating Site

The Participating Site is solely responsible for the management of the trial within their site. This includes ensuring local management approval has been given, ensuring the trial is conducted according to GCP requirements, and ensuring the appropriate insurance or indemnity is in place. The Participating Site is also responsible for arranging access for on-site monitoring and auditing as identified in the trial protocol and also for regulatory inspections.

16.7 Principal Investigator (PI)

The PI is responsible for the delegation of trial activities within their site and ensuring all personnel are adequately trained and qualified to carry out their responsibilities. The PI will be required to provide evidence of GCP training (usually a certificate) or undergo the required GCP training. Regarding the management of patients within their site, the PI is responsible for the safety and well being of trial patients, reporting any deviations from the protocol to the coordinating trial office as well as any SAEs or safety issues. Full details of the responsibilities of the PI are outlined

in the Clinical Trial Agreement. Two original copies of this will be held – one with the Sponsor(s) and the other at the participating site. A photocopy of the signed agreement will also be held at the CRUK Glasgow CTU.

16.8 Central Monitoring

Trial sites will be monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. Trial staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have.

16.9 On-Site and Telephone Monitoring

16.9.1 Telephone Monitoring

All participating sites will be monitored remotely by telephone prior to being subject to an on-site monitoring visit. This will involve site staff providing verification of site file contents, drug accountability and source data during the telephone call. Investigators and site staff will be notified in advance about forthcoming monitoring calls.

16.9.2 On-Site Monitoring

All participating trial sites will be monitored by the CRUK Glasgow CTU on behalf of the Sponsor(s) by site visit. The PI will allow the Clinical Trial Monitor access to source documents as requested. In addition, the pharmacy department responsible for the trial will be visited to allow monitoring of the pharmacy site file and review of security, storage and accountability of trial drugs (if applicable). Investigators and site staff will be notified in advance about forthcoming monitoring visits. On occasion, members of the CRUK Glasgow CTU monitoring team may be accompanied by other staff from the unit for training purposes. Where a participating site is using electronic data reporting systems or electronic patient records and hard copies are not available, the CRUK Glasgow CTU monitor will require access to a computer for the duration of the visit in order to verify all relevant source data against the case report forms. This may involve being given a temporary log-in. If this is not permitted by local policy, there must be a member of site staff available to provide access to the monitor.

14 PUBLICATION POLICY

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. It will provide collaborators the International Committee of Medical Journal Editors (ICMJE) criteria will be used to ensure all those who have contributed to the trial are appropriately acknowledged.

The Experimental Drug Lead will be responsible for the primary study manuscript and will be lead author for the part of ATLANTIS that relates to their novel drug. The ATLANTIS Chief Investigators will usually be given the last author position.

No site or individual will publish data without prior approval of the TMG.

The data arising from ATLANTIS will belong to the trial Co-Sponsors NHS Greater Glasgow & Clyde and the University of Glasgow. The TMG shall act as custodian of this data.

17 REFERENCES

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18 APPENDIX I – PERFORMANCE STATUS (ECOG)

The following table presents the ECOG performance status scale:

GRADE	
0	Fully active and able to carry on all pre-disease performance without restriction. (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20).

* As published in Am. J. Clin. Oncol.:*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

19 APPENDIX II – TNM CLASSIFICATION

19.1 TNM definitions[1]

	T - Primary tumour
X	Primary tumour cannot be assessed
0	No evidence of primary tumour
a	Non-invasive papillary carcinoma
is	Carcinoma in situ (i.e., flat tumour)
1	Tumour invades subepithelial connective tissue
2	Tumour invades muscularis propria: ▪ pT2a: Tumour invades superficial muscularis propria(inner half) ▪ pT2b: Tumour invades deep muscularis propria (outer half)
3	Tumour invades perivesical tissue: pT3a: Microscopically ▪ pT3b: Macroscopically (extravesical mass)
4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, bladder, abdominal wall ▪ T4a: Tumour invades prostate stroma, seminal vesicles, uterus or vagina ▪ T4b: Tumour invades pelvic wall or abdominal wall
	N- Regional lymph nodes
X	Regional lymph nodes cannot be assessed
0	No regional lymph node metastasis
1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral
2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
3	Metastasis in a common iliac lymph node(s)

	M- Distant metastasis
0	No distant metastasis
1	• M1a: Non-regional lymph nodes • M1b: Other distant metastasis

[1] TNM Classification of Malignant Tumours: International Union Against Cancer 8th Edition

20 APPENDIX III – NCI-COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Please go to the following website to access the NCI-CTCAE Version 4.03: June 14, 2010:
http://www.crukctuglasgow.org/media/CTCAE/CTCAE_4.03_2010-Jun-14.pdf

21 APPENDIX IV – RECIST CRITERIA FOR ANTITUMOUR RESPONSE

(RECIST Version 1.1, January 2009)

Please go to the following website to access RECIST Version 1.1, January 2009:

http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

22 APPENDIX V - CABOZANTINIB

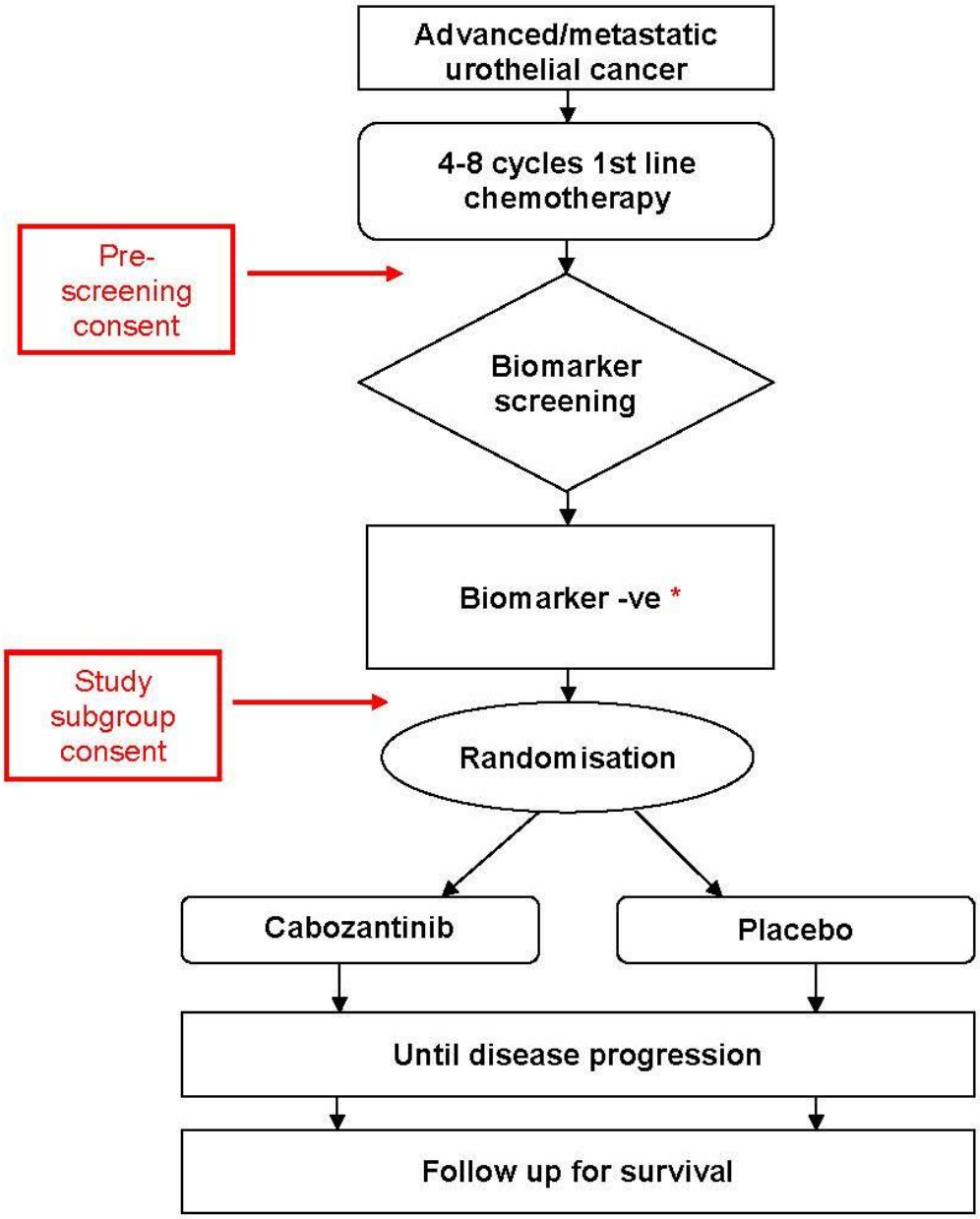
****PLEASE NOTE THAT ALL INFORMATION CONTAINED IN THIS APPENDIX IS *IN ADDITION* TO THAT CONTAINED IN THE MAIN BODY OF THE ATLANTIS PROTOCOL****

Trial Summary

Title:	**ATLANTIS-1 (Cabozantinib)**
Trial Drug:	Cabozantinib
Trial Drug Background:	There is a wide body of preclinical evidence supporting the relevance of MET and VEGF as anti-cancer targets in UC (1-4). Cell line work shows that MET is associated will cell line proliferation and growth (3). VEGF has also been extensively investigated in UC. It is also over expressed and associated with proliferation/growth in UC (1). The clinical data on VEGF targeting in UC in inconclusive (5, 6). Therefore the combination of MET and VEGF is attractive in metastatic UC. Cabozantinib is a combined MET and VEGF targeted TKI. Cabozantinib has significant activity and a license in Europe to treat medullary thyroid cancer (7). Pivotal renal cancer studies testing cabozantinib are also positive *(EudraCT NUMBER: 2013-001010-14).* It has shown early signs of activity in an on-going phase II trial in advanced UC (8). In this phase II study based in the NCI (USA) 55 patients with pretreated UC were treated with the drug. The majority of patients gained clinical benefit [cabozantinib (between 40 and 60 mg)]. The drug appears well tolerated at 40mg PO OD (the dose for ATLANTIS). Toxicity was typical for a VEGF targeted therapy, focusing on lethargy, diarrhoea, hypertension and hand/foot syndrome (7). There is currently a lack of data on the expression of MET or VEGF as a biomarker for cabozantinib activity. For this reason all ongoing and previous trials have not selected patients based on MET expression.
Treatment:	Patients who do not over express an ATLANTIS target biomarker will receive either cabozantinib at 40mg or placebo in a double blind manner (n=140).

	Treatment will continue until progression. Both dose reductions and treatment breaks for toxicity will be permitted (see section 4.7).
Duration:	140 patients recruited over 65 months with 4 months follow-up post recruitment end should provide the 114 events for this trial component.

Flow chart



* Or no other suitable ATLANTIS study subgroup available. Entry to this subgroup is not restricted by biomarker outcome.

Figure 1: Cabozantinib flow chart

Schedule of Assessments – Cabozantinib/placebo subgroup

Procedure/ Assessment	Pre-Screen	Subgroup Screening		Study Treatment (4 weekly intervals)														Follow-up	
		≤4 weeks	≤1 week	Week 1	Week 5	Week 9	Week 13	Week 17	Week 21	Week 25	Week 29	Week 33	Week 37	Week 41	Week 45	Week 49	Week 53+(19)	End of Treatment (12)	Off study treatment until progression (11)
Trial Procedures																			
Informed consent	X(1)	X(2)																	
Randomisation to subgroup			X																
Review of Eligibility Criteria		X																	
Demographic details	X(3)																		
Tumour characteristics and previous therapies	X(3)	X																	
Medical history		X																	
Physical examination(13)		X																X	
Skin toxicity assessment(16)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smoking History		X																	
ECOG performance status	X(3)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs(5)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test(6)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG (12-lead)(14)		X			X		X			X			X			X		X	
Toxicity/symptoms/ adverse events assessment	X(3)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments																			

Full blood count	X[3]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	
Serum biochemistry	X[3]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	
Translational blood sample	X				X[4]													X[4]	
Estimated GFR	X[3]		X																
Urinalysis and urinary protein assessment[15]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumour specimen sent for central analysis [4]	X																		
Radiological Assessments																			
CT scan of chest, abdomen, pelvis		X[8]					X[8]			X[8]			X[8]			X[8]		X	X[10]
Treatment																			
Cabozantinib/placebo [17]				X[18]	X	X	X	X	X	X	X	X	X	X	X	X	X		

This schedule demonstrates the appointments/procedures for the cabozantinib/placebo group ONLY. Please refer to individual IMP appendices for specific schedules and other visits for other treatments groups within the ATLANTIS trial.

(1) Patients should have signed and dated informed consent for pre-screening.

(2) 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.

(3) 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.

(4) Tumour samples and all other translational samples should be sent for the attention of Sakunthala Kudahetti, Barts Cancer Institute 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, subject to patient consent. Individual samples will be returned at the end of the trial on request. Samples will be processed in accordance with the ATLANTIS lab manual.

(5) Weight, height, pulse and blood pressure

(6) Human chorionic gonadotropin (HCG) results must be obtained and reviewed before the first dose of IMP is administered for women of reproductive potential. Pregnancy test to be repeated every 4 weeks in female patients of reproductive potential until trial treatment stops.

(7) Haematology including full blood count with WBC, ANC (absolute neutrophil count), platelet count and haemoglobin. Biochemistry including sodium, adjusted calcium, phosphate, magnesium, potassium, AST, ALT, alkaline phosphatase (AP), LDH, TSH, T4, bilirubin, creatinine, protein and albumin. Prothrombin time (PT) orINR, partial thromboplastin time (PTT) and amylase are required within 7 days of randomisation only.

(8) All patients should have abdominal and pelvic CT or MRI, plus CT scan of the thorax. Patients should have baseline scanning then every 12 weeks until week 49 (+/- 2 weeks), then every 16 weeks (+/- 2 weeks) to week 97 then every 24 weeks (+/- 2 weeks) during trial treatment or after completion of treatment if terminated prior to disease progression, until closure of this individual drug subgroup.

(9) Patients who come off the trial drug should have tumour assessments within 4 weeks of coming off cabozantinib/placebo, irrespective of whether or not the patient is still being followed up for progression.

(10) Patients who come off the trial drug should have tumour measurements where they have not been completed within the past 4 weeks. This includes abdominal and pelvic CT or MRI, plus chest CT scan. Patients who stop treatment for whatever reason before progressive disease is documented will continue to have scans at 12-weekly, 16-weekly or 24-weekly intervals as previously, until closure of this individual drug subgroup.

(11) Follow-up visits after progression will continue at the investigators discretion until death, or until closure of this individual drug subgroup. Future treatment and cause of death must be recorded on the eCRF.

(12) Must be performed within 4 weeks of stopping trial treatment.

(13) Physical examination should be performed during the screening visit (within 4 weeks prior to randomisation) and at the end of treatment visit. Additional physical examinations are only required as clinically indicated.

(14) Patients should have ECG at screening and at week 5, week 13 and every 12 weeks thereafter. Should be repeated as clinically indicated.

(15) Patients should have urinary protein creatinine ratio (UPCR) assessment within 4 weeks prior to randomisation, and at each treatment visit.

(16) Skin toxicity assessment to include patient history, examination and documentation of reported skin changes.

(17) Cabozantinib or placebo dispensed every 28 days (28 day treatment cycle).

(18) Cabozantinib or placebo dosing must start within 3 days after randomisation.

(19) Continues every 4 weeks whilst on treatment.

1 INTRODUCTION

1.1 Background

1.1.1 Rationale

The purpose of this subgroup of the ATLANTIS trial is to test if combined MET and VEGF inhibition can improve progression free survival (compared to placebo) in unselected patients with advanced or metastatic bladder cancer who have recently completed first line chemotherapy.

There is a wide body of preclinical evidence supporting the relevance of MET and VEGF as anti-cancer targets in UC (1-4). Cell line work shows that MET is associated will cell line proliferation and growth (3). VEGF has also been extensively investigated in UC. It is also over expressed and associated with proliferation/growth in UC (1). The clinical data on VEGF targeting in UC in inconclusive (5, 6). Therefore the combination of MET and VEGF is attractive in metastatic UC.

Cabozantinib is a combined MET and VEFG targeted TKI. Cabozantinib has significant activity and a license in Europe to treat medullary thyroid cancer (7). Pivotal renal cancer studies testing cabozantinib are also positive (EudraCT NUMBER: 2013-001010-14).

It has shown early signs of activity in an on-going phase II trial in advanced UC (8). In this phase II study based in the NCI (USA) 55 patient with pretreated UC were treated with the drug. The majority of patients gained clinical benefit [cabozantinib (between 40 and 60 mg)]. The drug appears well tolerated at 40mg PO OD (the dose for ATLANTIS). Toxicity was typical for a VEGF targeted therapy, focusing on lethargy, diarrhoea, hypertension and hand/foot syndrome (7). There is currently a lack of data on the expression of MET or VEGF as a biomarker for cabozantinib activity. For this reason all ongoing and previous trials have not selected patients based on MET expression.

In ATLANTIS patients who do not over express a target biomarker (such as AR) will receive either cabozantinib at 40mg or placebo in a double blind manner. An important exploratory objective in this group of patients will be to discover predictive nature of MET and VEGF for cabozantinib in UC (MET, measured by immunohistochemistry).

2 TRIAL DESIGN

PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL INCLUSION/EXCLUSION CRITERIA

2.1 Inclusion Criteria

1. Able to swallow study drug

2. Organ and marrow function and laboratory values as follows within 7 days before the first dose of cabozantinib:

a. ANC ≥1.5 x 10^9/L (without colony stimulating factor support);
b. Platelets ≥100 x 10^9/L ;
c. Haemoglobin ≥ 9 g/dL;
d. Bilirubin ≤ 1.5 × ULN. For subjects with known Gilbert's disease, bilirubin ≤ 3.0 x ULN.
e. ALT and AST ≤ 3.0 × ULN;
f. Serum albumin ≥ 28 g/l;
g. Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation or Wright formula should be used:
   Cockcroft and Gault equation
   i. Male: CrCl (mL/min) = 1.23 x(140 - age) × weight (Kg) / (serum creatinine umol/L);
   ii. Female: 1.04 x(140 - age) x weight (Kg)/ (serum creatinine umol/L)
   Wright formula - Without CK using Jaffe serum creatinine
   Estimated GFR (ml/min)= {[6580 – (38.8 x age)] x BSA x [1- (0.168 x sex)]} serum creatinine umol/L (where sex: male= 0 and female= 1, body surface area (BSA): Du Bois)
h. Amylase < 2.0 x ULN and no radiologic or clinical evidence of pancreatitis;
i. Urine protein to creatinine ratio (UPCR) ≤ 113.1 mg/mmol (1mg/mg) or total urinary protein <1gram/24 hours. Patients with residual tumour in the urothelial tract will be considered suitable as long as there are no other features of protein-losing nephropathy, such as hypoalbuminaemia (<25g/l) or significant oedema.
j. Serum phosphate, adjusted calcium, magnesium and potassium ≥ LLN.
k. Prothrombin time (PT) or INR; and partial thromboplastin time (PTT) test ≤ 1.3 x ULN

3. Sexually active subjects (men and women) must use highly effective methods of contraception (eg, male or female condom) during the course of the study and for 4 months after the last dose of study drug, even if oral contraceptives are also used. Acceptable forms of contraception are described in section 9.3 of the main protocol.

2.2 Exclusion Criteria

1. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomisation.

2. Receipt of any type of anticancer antibody (including investigational antibody) within 4 weeks before randomisation.

3. Previous MET or VEGF targeted therapy.

4. Radiation therapy within 4 weeks before randomisation (palliative radiotherapy ≥2 weeks prior to trial entry is permitted). Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment.

5. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (e.g., warfarin, direct thrombin) or platelet inhibitors (e.g., clopidogrel). Low-dose aspirin for cardioprotection (per local applicable guidelines) is permitted and Factor Xa inhibitors are permitted following initial study treatment.

6. Uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

- Cardiovascular disorders:
    i. Congestive heart failure New York Heart Association class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
    ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.
    iii. Stroke (including TIA), myocardial infarction, or other ischemic event, or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism, subjects with a venous filter (eg, vena cava filter) are not eligible) within 6 months before randomisation.
    iv. Any history of long QT syndrome;

- Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
    i. Tumours invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.
    ii. Abdominal fistula, gastrointestinal perforation, bowel obstruction, clinically significant GI bleeding, or intra-abdominal abscess (Complete healing of an intra-abdominal abscess must be confirmed) within 6 months before randomisation.

- Clinically significant haematemesis, or haemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary haemorrhage) within 3 months before randomisation.

- Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

- Lesions invading major pulmonary blood vessels.

- Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before the first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment.

- Other clinically significant disorders such as:
    i. Active infection requiring systemic treatment, infection with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)- related illness, or chronic hepatitis B or C infection.
    ii. Serious non-healing wound/ulcer/bone fracture.
    iii. Malabsorption syndrome.
    iv. Uncompensated/symptomatic hypothyroidism.
    v. Moderate to severe hepatic impairment (Child-Pugh B or C).
    vi. Requirement for haemodialysis or peritoneal dialysis.
    vii. History of solid organ transplantation.

7. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 1 month before randomisation. Minor surgery (including uncomplicated tooth extractions) within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment is permissible. Patients with clinically relevant ongoing complications from prior surgery are not eligible.

8. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 msec within 10 days before randomisation. Two ECGs must be performed, at least 3 minutes apart. If the average of these results for QTcF is ≤ 500 msec, the patient meets eligibility in this regard.

9. Previously identified allergy or hypersensitivity to components of the study treatment formulations.

10. Received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (eg, cytokines or antibodies) within 3 weeks, or nitrosoureas/mitomycin C within 6 weeks before the first dose of study treatment.

11. Prior treatment with cabozantinib.

12. Requires chronic concomitant treatment with strong CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort), or strong CYP3A4 inhibitors (eg ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir).

*****PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL INCLUSION/EXCLUSION CRITERIA*****

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria should be addressed via contact with the CTU prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply.

3 Trial Procedures

3.1 Screening Procedures

The following is required within 4 weeks of randomisation in addition to those listed in the main protocol:

Urinary protein-creatinine ratio

Skin toxicity assessment

The following is required within 7 days of randomisation in addition to those listed in the main protocol:

Biochemistry also to include calcium, phosphate, magnesium, amylase, TSH and T4

The screening laboratory determinations can be used as week 1 pre-dose blood tests as long as they are not >7 days prior to first administration of trial treatment. If >7 days prior to first administration of trial treatment then the specified blood tests for week 1 should be repeated.

3.2 Procedures at each visit on trial drug/placebo (see schedule of assessments table, page 2)

Additional tests required over and above those listed in the main protocol:

Biochemistry also to include calcium, phosphate, magnesium, TSH and T4

Urinary protein-creatinine ratio (UPCR)

Pregnancy test (for female patients of child bearing potential only)

ECG at week 5, week 13 and every 12 weeks thereafter

Skin toxicity assessment

3.3 Radiological Investigations Every 12 Weeks

There are no additional imaging tests required over and above those listed in the main protocol.

3.4 End of Trial Procedures

Additional procedures required over and above those listed in the main protocol:

ECG

Skin toxicity assessment

3.5 Follow-Up

There are no additional procedures required over and above those listed in the main protocol.

4 TREATMENTS

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

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.

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.

4.1 Specific Drug Information

4.1.1 Cabozantinib

Cabozantinib and placebo are considered IMPs for the purposes of this trial.

Cabozantinib is supplied as film coated tablets at the dosage strength of 20mg or identical matched placebo. Packed in high density polyethylene, child resistant and tamper evident bottles, each containing 30 tablets. For continuous daily dosing until progression. Refer to Cabozantinib Investigator Brochure for information regarding the physical and chemical properties of cabozantinib and a list of excipients. Cabozantinib and placebo should be stored at controlled room temperature at 20- 25˚C.

4.1.1.1 Cabozantinib/ Placebo Dispensing, Accountability and Administration

The investigator or a delegated individual (e.g. pharmacist) must ensure that the trial drugs (IMP and NIMPs) are dispensed in accordance with the protocol, local Standard Operating Procedures and applicable regulatory requirements. Each prescription will cover one cycle (28 days) of cabozantinib or placebo.

4.1.1.2 Cabozantinib/Placebo Dispensing and Accountability

Bottle number, batch number, dose prescribed, quantity and expiry of the drug supplied must be recorded in the accountability logs. Both bulk stock and individual patient accountability logs must be completed.

Patients will be required to return all bottles (including empty bottles) of trial medication at the next dispensing visit and again upon the completion of treatment. Any remaining tablets must be documented in the accountability logs. Any evidence of non-compliance with the prescribed dosing must be reported to the local PI. Any potential patient medication compliance issues should be addressed in a timely manner.

Full instructions regarding management, labelling and accountability of cabozantinib/placebo is given in the IMP Management and Accountability Document (Cabozantinib) for the trial.

4.1.1.3 Cabozantinib/Placebo Administration

The start of cabozantinib or placebo dosing should occur within 3 days after randomisation. Patients in the cabozantinib arm will take the cabozantinib or placebo dose once daily. Doses will be self-administered at home once-daily at the same time each day. The assigned dose is 40 mg cabozantinib or placebo given once daily. A dose of 40 mg should be maintained in the absence of treatment-emergent toxicity.

Patients should fast (with the exception of water) for at least 2 hours before taking their medication. After the 2-hour fast, patients are to take medication with a full glass of water (approximately 8 ounces or 230mls) with no more food intake for one hour post-dose. The patient should take cabozantinib or placebo at approximately the same time every day and should adhere to the fasting requirements described in this section. Tablets should be swallowed whole and not crushed or chewed.

Patients should be instructed to not make up vomited doses and to maintain the planned dosing schedule. Patients should not make up for missed doses if more than 12 hours have elapsed after the time the patient would usually take the dose. In the event of missed doses, patients should not take 2 doses to make up for the one missed. Grapefruit and Seville oranges may increase plasma concentrations of cabozantinib and should be avoided.

4.1.1.4 Cabozantinib/Placebo Supplies

Cabozantinib or identically matched placebo will be supplied free of charge by Exelixis for use by patients in this trial and will be trial-specific investigational medicinal product trial stock. These will be shipped to site directly from CSM Clinical Supplies Management Europe, Germany.

- Packaging, labelling and preparation of cabozantinib and placebo will be performed in a way that will ensure blinding throughout the trial.
- Labelling of the cabozantinib and placebo will be performed in accordance with Good Manufacturing Practice and in accordance with local labelling requirements. The labels will contain information to meet the applicable regulatory requirements.
- Only those supplies intended for use in the trial should be dispensed to the trial participants and clinical trial supplies must be dispensed in accordance with the trial protocol.
- Upon arrival of investigational product at site, site personnel should check the supplies for damage and verify proper identity, quantity, integrity of seals and temperature conditions and report any deviations or product complaints to the CRUK Glasgow CTU upon discovery.
- All trial medications must be stored in a secure area with access limited to the investigator and authorised site staff and under physical conditions that are consistent with the specific requirements of the medication. For batch specific instructions and information on the shelf life see the packaging.
- Full instructions regarding management, labelling and accountability of cabozantinib or placebo is given in a separate IMP Management and Accountability Document (Cabozantinib) for the trial.

4.1.1.5 Duration of Treatment

See section 6.11.1 of the main protocol.

4.2 Non-IMPs

There are no non-IMPs in this subgroup treatment schedule.

4.3 Supportive Medications

- Antiemetics and antidiarrheal medications are allowed for treatment or prophylaxis according to standard clinical practice if clinically indicated.
- Patients who develop plantar-palmer erythrodysaesthesia (PPE) on cabozantinib therapy should be treated as per local policy. Dose reductions and/or treatment interruptions may be considered for CTCAE grade≥3 or intolerable grade 2 PPE at the discretion of treating clinician.

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, ASCO or ESMO guidelines).
- Drugs used to control bone loss (eg, bisphosphonates and denosumab) can be continued if started before randomization and the benefit outweighs the risk per the investigator's discretion Note: After randomization, the use of these drugs requires Sponsor approval with the exception of management of disease related hypercalcemia in emergency situations. However, this should subsequently be reported to the Sponsor for acknowledgement and post-initiation approval.
- Transfusions, hormone replacement, and short term higher doses of corticosteroids (above the physiologic replacement dose) should be utilized as indicated by standard clinical practice.
- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively.

4.4 Concomitant Therapy

*****PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL INFORMATION ON CONCOMITANT THERAPY*****

4.5 Prohibited Therapy

The following therapies are prohibited until study treatment has been permanently discontinued:

• Therapeutic doses of oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines). Direct factor FXa inhibitors are permitted if indicated after initiation of study treatment.

• Radiation therapy prohibited during study treatment (palliative radiotherapy may be permitted- please contact CTU Glasgow to discuss).

• Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).

• Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort)

may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

• Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir and cannabinoids) may increase cabozantinib concentrations and should be avoided. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

*****PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL INFORMATION ON PROHIBITED THERAPY*****

4.6 Interactions with other medications

Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the AUC of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared to CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction ofCYP1A1 at high cabozantinib concentrations (30 µM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not CYP2D6, CYP2C8, CYP2C19, CYP2B6 or CYP1A2 substrate). The chronic use of strong CYP3A4 inducers should be avoided (see section 4.5). Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Strong CYP3A4 inhibitors should be avoided (see section 4.5) and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to

cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:
Http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Protein Binding: Cabozantinib is highly bound (≥ 99.7%) to human plasma proteins. Therefore, highly protein bound drugs (such as diazepam, furosemide and propranolol) should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Administration of warfarin, a highly protein bound drug, at therapeutic doses is not permitted for patients receiving cabozantinib in this trial (see section 4.5).

Cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.

Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine) should be approached with caution.

Concomitant use of gastric pH modifying agents (ie. PPIs, H2 receptor antagonists and antacids) is not contraindicated in patients taking cabozantinib. Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

Food has been demonstrated to increase exposure levels of cabozantinib, so patients are advised to fast (with the exception of water) for at least 2 hours before taking their dose of cabozantinib. After the 2-hour fast, subjects are advised to take cabozantinib with a full glass of water (minimum of 8oz or 240ml) with no more food intake for one hour post-dose.

4.7 Dose modifications for treatment-emergent toxicity

Many adverse events can occur early (within the first few weeks) of treatment with cabozantinib e.g. diarrhoea and PPE, and should be managed with best supportive care at the earliest signs of toxicity. Substantial acute toxicities should be managed as medically indicated and with temporary suspension of cabozantinib as appropriate. Dose modifications for toxicities are allowed as clinically indicated by the treating physician.

Cabozantinib therapy should be discontinued for the following adverse events and should be discussed with Chief Investigator: visceral perforation or fistula formation, severe haemorrhage, serious arterial thrombo-embolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management and reversible posterior leukoencephalopathy syndrome (RPLE).

Management of treatment-emergent proteinuria

Proteinuria has been reported with cabozantinib and should be monitored by measuring urinary protein-creatinine ratio (UPCR) as per schedule of assessments (table 2). Table 3.0 provides treatment guidelines for proteinuria deemed to be related to cabozantinib. Cabozantinib should be discontinued in patients who develop nephrotic syndrome (proteinuria >3.5 grams per day, low serum albumin, high serum cholesterol and clinical oedema).

Table 3.0. Management of proteinuria related to cabozantinib

Severity of proteinuria (UPCR)	**Management guideline**
UPCR ≤ 113.1mg/mmol) (≤ 1mg/mg)	No change in cabozantinib treatment or monitoring.
UPCR > 113.1 and < 395.9 mg/mmol (>1 and <3.5 mg/mg)	Consider confirming with 24-hour urinary protein collection or repeat UPCR No change to cabozantinib treatment if urinary protein ≤2g/24 hours on urine collection. Consider dose reduction or treatment interruption if UPCR≥226.2mg/mmol 2mg/mg on repeat UPCR testing or urinary protein >2g/24 hours on urine collection. Restart cabozantinib on a reduced dose if UPCR decreases to ≤226.2mg/mmol. Consider with-holding cabozantinib treatment if UPCR remains ≥226.2mg/mmol

	despite a dose reduction. Repeat UPCR within 7 days and weekly. If UPCR ≤ 113.1mg/mmol on 2 consecutive readings then UPCR monitoring can revert to protocol-specified times.
UPCR ≥ 395.9 mg/mmol (≥ 3.5mg/mg)	Withhold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urinary collection. If UPCR ≥ 395.9mg/mmol on repeat measurement, continue to withhold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to ≤226.2mg/mmol, re-start cabozantinib treatment at reduced dose and monitor UPCR weekly until it decreases to ≤ 113.1mg/mmol on 2 serial measurements. Further UPCR monitoring can revert to protocol-specified times.
Nephrotic syndrome	Discontinue study treatment and discuss with Chief Investigator.

Management of Hepatocellular toxicity

Elevation of AST, ALT and bilirubin have been observed during treatment with cabozantinib. Management guidance for hepatotoxicity related to cabozantinib is provided in the table below:

Severity of ALT, AST, Total Bilirubin elevations	**Recommended dose modification**
Grade 1	• Dose adjustment is usually not required • Consider discontinuing concomitant hepatotoxic medications and add supportive care as indicated
Grade 2	• Interrupt cabozantinib if lasting longer than 1 week and consider more frequent monitoring of ALT, AST and bilirubin • Re-start cabozantinib after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline

Grade 3 or greater	• Interrupt cabozantinib and consider more frequent monitoring of ALT, AST and bilirubin • Re-start cabozantinib at a reduced dose after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline • Discontinue if lab abnormalities cannot be reversed despite interruption of cabozantinib

The following condition requires discontinuation of cabozantinib:

- Drug-related ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN without other reasonable explanation, consistent with drug-induced liver injury (DILI).

Management of treatment-emergent Hypertension

It is recognised that some patients exhibit 'white-coat hypertension' during hospital visits. If the patient's blood pressure value taken during a hospital visit is high, then dose modification is not required if there is evidence documented by another healthcare professional (for example community nurse or general practitioner) of controlled blood pressure. Please refer to the following guidelines for management of drug-induced hypertension:

Event	**Recommended dose modification**
Persistently raised systolic blood pressure (SBP) >140mmHg and <160mmHg OR diastolic blood pressure (DBP) >90mmHg and <110mmHg.	• Optimise anti-hypertensive therapy by adding new or additional anti-hypertensive medications and/or increasing the dose of existing medications. • Reduce cabozantinib dose (see section 4.7.1) if optimal anti-hypertensive therapy (usually at least 3 agents) does

	not result in SBP <140mmHg or DBP<90mmHg. • If subject is symptomatic then interrupt cabozantinib therapy.
SBP ≥160mmHg and <180mmHg OR DBP ≥110 mmHg and <120mmHg	• Reduce cabozantinib by one dose level (see section 4.7.1) or interrupt study treatment, at clinician discretion. Cabozantinib therapy should be interrupted is patient is symptomatic of hypertension. • Add new or additional anti-hypertensive medications and/or increase the dose of existing medications. If optimised anti-hypertensive therapy (usually at least 3 agents) does not result in SBP <140mmHg or DBP <90mmHg, cabozantinib should be dose reduced or interrupted. • Re-start cabozantinib only if BP returns within parameters and is sustained (SBP<140mmHg and DBP <90mmHg)
SBP ≥ 180mmHg OR DBP ≥120mmHg OR symptomatic hypertension	• Stop cabozantinib therapy and optimise anti-hypertensive therapy. • Re-start cabozantinib at discretion of treating clinician once BP returns within acceptable parameters and is sustained (SBP <140mmHg and DBP <90mmHg)
Hypertensive emergency (Defined as uncontrolled elevated BP with clinical evidence	Discontinue cabozantinib

of progressive or impending end-organ damage, such as myocardial infarction, intracranial haemorrhage, encephalopathy, pulmonary oedema or renal dysfunction)	

Management of Palmar-plantar erythrodysesthesia syndrome (PPE)

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated subjects. All subjects on study should be advised to use prophylactic measures for skin care. These measures includes the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF ≥ 30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (e.g., abscess, cellulitis, or impetigo). Please refer to the following guidelines for management of PPE:

Severity of PPE	**Management Guideline**
Grade 1	Continue cabozantinib/placebo at current dose. Treat as per local policy. Assess subject at least weekly for changes in severity.
Grade 2	If tolerable, continue cabozantinib/placebo at current dose. If intolerable, reduce cabozantinib/placebo dose to next lower level and/or interrupt dosing. Treat as per local policy. If study treatment was interrupted (but not reduced), treatment may be restarted at the same dose or at one dose level lower when reaction decreases to Grade 1 or 0. If a study treatment interruption is again required, the dose must be reduced when treatment resumes.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Treat as per local policy. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 6 weeks.

Osteonecrosis of the jaw (ONJ)

Events of osteonecrosis of the jaw (ONJ) have been observed with cabozantinib. Oral examinations are recommended before randomization to determine eligibility and periodically during the study. In addition, patients should be advised regarding oral hygiene practice and to quickly report symptoms to the investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended. For invasive dental procedures, cabozantinib treatment should be withheld at least 28 days prior to scheduled surgery, if possible. Dose adjustments may be needed to safely use drugs to control bone loss (such as bisphosphonates and denosumab) in combination with study treatment. If ONJ occurs, cabozantinib treatment should be held and should not be restarted until the condition has sufficiently healed and the Sponsor has approved the re-initiation of therapy.

Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula and intra-abdominal and pelvic abscess may be associated with cabozantinib and patients should be evaluated for potential risk factors. Complete healing following abdominal surgery and radiation therapy and/or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Haemorrhage

Haemorrhagic events, including serious and sometime fatal events, have been reported with cabozantinib. Patients should be evaluated for potential bleeding risks factors prior to starting cabozantinib. Complete healing from radiation-induced side effects should have occurred before initiating cabozantinib treatment and cabozantinib should be discontinued in patients with serious and life-threatening bleeding events or recent haemoptysis.

Additional details regarding toxicities and their management can be found in the cabozantinib IB.

4.7.1 Dose Reductions

Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

A maximum of one dose reduction is allowed, as per table 4.1 below:

Table 4.1 Dose Reductions

Dose level	**Cabozantinib/placebo dose**	**Re-escalation Details**
Starting dose	40 mg/day (2 tablets)	
First dose reduction	20 mg/day (1 tablet)	Dose re-escalation is not permitted.

The dose may be reduced (to 20mg of cabozantinib/placebo) 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. Discussion with the Chief Investigators for dose reductions is advised but not mandated.

4.7.2 Dose Interruptions

Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities, and consideration should be given to a dose reduction as outlined in 4.7 and 4.7.1 when toxicity resolves to grade 1 or baseline.

Patients should have cabozantinib/placebo interrupted immediately unless the following criteria are met:

- Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor.
- Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.

Patients may interrupt treatment for up to 28 days. Dose interruptions of >14 days should be reported to the Sponsor. Cessation of therapy for >28 days due to treatment related toxicity should result in permanent drug discontinuation. If the patient is to undergo planned surgery, including dental surgery, during the trial, and cabozantinib is anticipated to be interrupted for > 28 days this must be discussed first with the Chief Investigator or delegate prior to entry into the main study. In the event of dose delays, radiological assessments should remain on schedule and

be performed in line with the protocol schedule, regardless of the number of cycles of treatment received by the patient. Care should be taken to record all dose modifications accurately.

4.8 Emergency Unblinding

All Principal Investigators and/ or members of staff delegated to unblind patients will have access via the unblinding system that allows them to break the blind for an individual patient in an emergency situation as described above.

Site personnel will access the unblinding system via a secure website, using individual access codes. Trial specific user guides and PIN details will be sent to each site after initiation.

The telephone line for the unblinding system helpdesk is 0141 330 4744. Please note that the unblinding system helpdesk are only able to provide assistance with the function of the system, and this is service is provided Monday- Friday 9am- 5pm. Please state 'ATLANTIS-1 Unblinding System Issue' when contacting the helpdesk. Each site must have arrangements in place to cover unblinding 24 hours each day.

4.9 Unblinding Following Final Analysis

All patients ongoing at the time of final analysis will be unblinded and informed in sufficient time for ongoing access arrangements to be made by the investigator, if considered in the patient's best interests. Trial IMP supply will stop completely once these arrangements are in place.

5 TRANSLATIONAL RESEARCH

An important exploratory objective in this group of patients will be to discover predictive nature of MET and VEGFR2 for cabozantinib in UC (MET, measured by immunohistochemistry).
Germ line material will be taken for SNP analysis and free circulating tumor DNA and plasma will be collected. Samples will be processed in accordance with the ATLANTIS lab manual.

6 SAFETY REPORTING

6.1 Recording of Adverse Events and Serious Adverse Events

In addition to details given in section 9.2.1.2 (Recording of Adverse Events) in the main body of the protocol, for patients receiving cabozantinib, all AEs and SAEs must be recorded/reported from

cabozantinib subgroup consent and followed until resolution, or for 30 days after discontinuation of cabozantinib treatment, whichever comes first, or until toxicity has resolved to baseline or ≤ grade 1, or until the toxicity is considered to be irreversible.

6.2 Pregnancy – Duration of Contraception and Follow-Up for Pregnancy

In addition to the information provided in Section 9.3 (Pregnancy) in the main body of this protocol, all advice regarding contraception and follow-up for pregnancy applies for 4 months following the last administration of cabozantinib.

6.3 Reference Safety Information

Appendix K of the Investigator Brochure for cabozantinib will act as the RSI for this subgroup of the trial.

7 STATISTICS AND DATA ANALYSIS

7.1 Trial Design and Sample Size

The general study design can be found in the main protocol section 11.1.

For this component patient will be randomized between cabozantinib and placebo (1:1). The median PFS on the placebo arm is estimated to be 6 months. The comparison between the arms is designed to detect an improvement to a median PFS of 9 months with cabozantinib (this corresponds to a hazard ratio of 0.67; this size of difference is appropriate for a new agent in an untargeted population). This requires 114 PFS events. Assuming a recruitment rate of 70 patients per year, 140 patients recruited over 24 months with 8 months follow up post recruitment end should provide this number of events.

This number also provides >90% power (10% one sided) to detect between the study arms a difference in the reduction in size of measurable disease corresponding to a standardised effect size of 0.5.

7.2 Analysis Plan

As per section 11.2 of main protocol.

Due to early closure of the trial, analysis is planned to take place after 50 PFS events have been observed, and to not undertake any interim analyses. This provides 72.3% power with 20% (one

sided) alpha.

8 REGULATORY

8.1 Funding

This drug arm within the ATLANTIS umbrella trial structure is funded by an educational grant from Exelixis. Please refer to the site agreement for full information on any per patient/site payments.

9 REFERENCES

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23 APPENDIX VI - RUCAPARIB

****PLEASE NOTE THAT ALL INFORMATION CONTAINED IN THIS APPENDIX IS *IN ADDITION* TO THAT CONTAINED IN THE MAIN BODY OF THE ATLANTIS PROTOCOL****

Trial Summary

Title:	**ATLANTIS-2 (Rucaparib)**
Trial Drug:	Rucaparib
Trial Drug Background:	Emerging data is consistent for a subgroup of patients with urothelial cancer (UC) exhibiting DNA repair deficiency phenotype resulting from defects in a variety of genes including BRCA1, BRCA2, BAP1, ATM, PALB2, FANCD2, ERCC2.[1, 2] These DNA repair gene defects predict for benefit following cisplatin based chemotherapy in UC implying that a switch maintenance therapy strategy for PARP inhibition after prior chemotherapy benefit may allow for enrichment of a 'BRCA-like' subgroup. PARP inhibition is active against multiple bladder cancer cell lines and xenografts.[3] Evidence supports development of PARP inhibition in patients with either BRCA1 or BRCA2 mutations, either as a somatic or germline event, and in addition a wider selected group with evidence of homologous recombination deficiency (HRD) associated cancers.[4, 3, 5-6] PARP inhibitors, including rucaparib, have been extensively investigated and exhibit clinical activity in various platinum sensitive cancers.[7,8, 13] Data exist to support a hypothesis that biomarker selection either for BRCA1 or BRCA2 mutation (both germline and wild-type) or a wider BRCA-like group of patients allows for exploitation of synthetic lethality and for patient stratification strategies to be developed.[13]. To date PARP inhibition has not been tested in UC. Taken together, these data imply that BRCA1/2 mutant and/or HRD associated UC subgroup would be relevant for investigation of a PARP inhibitor. Patients

	with mutations in a defined HRD gene panel which includes BRCA1 or BRCA2, and/or high %LOH within their archival diagnostic/surgical sample would be eligible for entry to the rucaparib comparison arm of ATLANTIS. These patients would be defined within the study as HRD biomarker positive. 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 and BRCA2 homozygous mutant cell lines.
Treatment:	Patients who are HRD biomarker positive at pre-screening will receive either rucaparib 600mg twice daily or matched placebo (n=48). Treatment will continue until progression. Both dose reductions and treatment breaks for toxicity will be permitted (see section 4.7).
Duration:	48 patients recruited over 37 months with 8 months follow-up post recruitment end should provide the 39 events for this trial component.

Flow chart

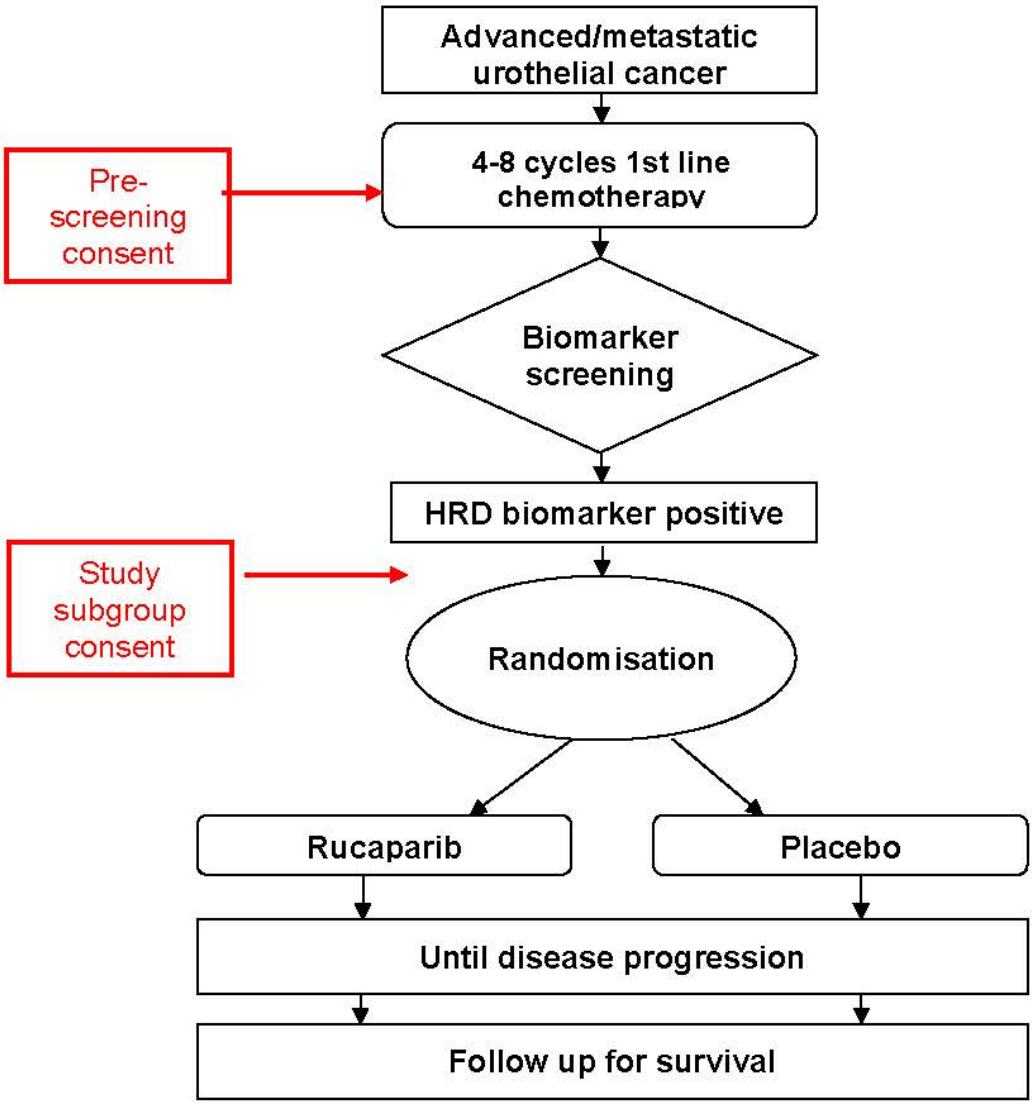

Figure 1: Rucaparib flow chart

Schedule of Assessments – Rucaparib/placebo subgroup

Procedure/ Assessment	Pre-Screen	Subgroup Screening		Study Treatment (4 weekly intervals)														Follow-up	
		≤4 weeks	≤1 week	Week 1	Week 5	Week 9	Week 13	Week 17	Week 21	Week 25	Week 29	Week 33	Week 37	Week 41	Week 45	Week 49	Week 53+[17]	End of Treatment[12]	Off study treatment until progression[11]
Trial Procedures																			
Informed consent	X[1]	X[2]																	
Randomisation to subgroup			X																
Review of Eligibility Criteria		X																	
Demographic details	X[3]																		
Tumour characteristics and previous therapies	X[3]	X																	
Medical history		X																	
Smoking History		X																	
Physical examination[13]		X																X	
ECOG performance status	X[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[5]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[6]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG (12-lead)		X																	
Toxicity/symptom/ adverse events assessment	X[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments																			
Full blood count	X[3]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	

Serum biochemistry	X[3]		X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7, 14]	X[7]	
Translational blood sample	X				X[4]													X[4]	
Estimated GFR	X[3]		X[7]																
Tumour specimen sent for central analysis [4]	X																		
Radiological Assessments																			
CT scan of chest, abdomen, pelvis		X[8]					X[8]			X[8]			X[8]			X[8]		X	X[10]
Treatment																			
Rucaparib/ placebo[15]				X[16]	X	X	X	X	X	X	X	X	X	X	X	X	X		

This schedule demonstrates the appointments/procedures for the rucaparib subgroup ONLY. Please refer to individual IMP appendices for specific schedules and other visits for other treatment subgroups within the ATLANTIS trial.

[1]Patients should have signed and dated informed consent for pre-screening.

[2]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 observation.

[3]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.

[4]Tumour samples and all other translational samples should be sent for the attention of Sakunthala Kudahetti, Barts Cancer Institute 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, subject to appropriate consent. Individual samples will be returned at the end of the trial on request. Samples will be processed in accordance with the ATLANTIS lab manual.

[5]Weight, height, pulse and blood pressure

[6]Human chorionic gonadotropin (HCG) results must be obtained and reviewed before the first dose of IMP is administered for women of child bearing potential.

[7]Haematology including full blood count with WBC, ANC (absolute neutrophil count), platelet count and haemoglobin. Biochemistry including sodium, calcium, phosphate, magnesium, potassium, AST, ALT, alkaline phosphatase (AP), LDH, bilirubin, creatinine, protein and albumin. Serum cholesterol is also required within 7 days of randomisation, and at every clinic visit whilst on study treatment.

[8]All patients should have abdominal and pelvic CT or MRI, plus CT scan of the thorax. Patients should have baseline scanning then every 12 weeks until week 49 (+/- 2 weeks), then every 16 weeks (+/- 2 weeks) to week 97 then every 24 weeks (+/- 2 weeks) during trial treatment or after completion of treatment if terminated prior to disease progression, until closure of this individual drug subgroup.

[9]Patients who come off the trial treatment should have tumour assessments within 4 weeks of coming off trial treatment, irrespective of whether or not the patient is still being followed up for progression.

[10]Patients who come off the trial treatment should have tumour measurements where they have not been completed within the past 4 weeks. This includes abdominal and pelvic CT or MRI, plus CT scan of the thorax. Patients who stop treatment for whatever reason before progressive disease is documented will continue to have scans at 12-weekly, 16-weekly or 24-weekly intervals as previously, until closure of this individual drug subgroup.

[11]Follow-up visits after progression will continue at the investigators discretion until death, or until closure of this individual drug subgroup. Future treatment and cause of death must be recorded on the CRF.

[12]Must be performed within 4 weeks of stopping trial treatment.

[13]Physical examination should be performed during the screening visit (within 4 weeks prior to randomisation) and at the end of treatment visit. Additional physical examinations are only required as clinically indicated.

[14]Serum cholesterol is also required within 7 days of randomisation, and at every clinic visit whilst on study treatment.

[15]Rucaparib or placebo dispensed every 28 days (28 day treatment cycle)

[16]Rucaparib or placebo dosing must start within 3 days after randomisation

[17]Continues every 4 weeks whilst on treatment.

1 INTRODUCTION

1.1 Background

1.1.1 Rationale

The purpose of this subgroup of ATLANTIS is to test whether PARP inhibition in selected patients with advanced or metastatic UC exhibiting DNA repair deficiency can improve progression-free survival (compared to placebo) after completion of first line chemotherapy.

Emerging data is consistent with a subgroup of patients with urothelial cancer (UC) exhibiting DNA repair deficiency resulting from defects in a variety of genes including BRCA1, BRCA2, BAP1, ATM, PALB2, FANCD2, ERCC2.[1, 2] These DNA repair gene defects may predict for benefit following cisplatin-based chemotherapy in UC.

PARP inhibition is active against multiple bladder cancer cell lines and xenografts.[3] Evidence supports development of PARP inhibition in patients with either BRCA1 or BRCA2 mutations, either as a somatic or germline event, and in addition a wider selected group with evidence of HRD signatures as evidenced by molecular testing.[4, 3, 5-6]

PARP inhibitors, including rucaparib, have been extensively investigated and exhibit clinical activity in various platinum sensitive cancers.[7,8,13] Data exist to support a hypothesis that biomarker selection either for BRCA1 or BRCA2 mutation (both germline and wild-type) or a wider BRCA-like group of patients allows for exploitation of synthetic lethality and for patient stratification strategies to be developed [14,15]. For example, rucaparib has been assessed in a single arm phase II study in ovarian cancer using BRCA1/ 2 mutation and a pre-specified cut point refinement for percentage genome-wide loss of heterozygosity (LOH) Compared to a BRCA wild-type/ low genomic LOH group, patients with either BRCA1/2 mutation or high genomic LOH had a hazard ratio for progression free survival of 0.25 (0.15- 0.42, $p<0.001$) and 0.51 (0.34- 0.74, $p<0.001$) respectively. [13] To date PARP inhibition has not been tested in UC.

Taken together, these data imply that a BRCA1/2 mutant and/or HRD associated UC subgroup would be relevant for investigation of a PARP inhibitor. Patients with mutations in a defined HRD gene panel which includes BRCA1 or BRCA2 and/or high %LOH ('HRD biomarker positive') would

be eligible for entry to the rucaparib comparison arm of ATLANTIS.

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 and BRCA2 homozygous mutant cell lines. Phase I and II clinical studies in patients with breast and ovarian/peritoneal cancer (CO-338-010 and ARIEL2) demonstrated that rucaparib is well tolerated and displays similar toxicity profiles to previous PARP inhibitor studies. Rucaparib is currently being evaluated in patients with other solid tumours, including metastatic pancreatic ductal adenocarcinoma with BRCA mutation (RUCAPANC) and maintenance treatment in patients with relapsed platinum-sensitive ovarian cancer (ARIEL3).[12] Rucaparib now has US approval for the treatment of women with relapsed BRCA-mutated ovarian cancer.

Safety pharmacology studies showed adverse effects of rucaparib on cardiovascular or central nervous systems at 5-fold (motor activity in rats) or 10 fold (in vitro hERG assay) higher than the clinical dose (600 mg BID). There were no significant gender differences or accumulation after repeat oral administration. Exposure increased in a dose-dependent manner in rats and dogs. In mice, rats, and dogs, the time to maximum plasma concentration (Tmax) and the absolute oral bioavailability (F) were 2 to 8 hours and 17% to 75%, respectively. In vitro plasma protein binding studies for humans was 70.2% at clinically relevant concentrations.

Rucaparib was rapidly and widely distributed in radio-distribution studies following IV administration consistent with a large volume of distribution. Little radioactivity was detected in brain. Activity was undetectable in most tissues by 96 hours. High levels of radioactivity were observed in ureters, bladder, and bile ducts, indicating both renal and biliary elimination routes.

In vitro studies indicated that rucaparib reversibly inhibited (decreasing potency) CYP1A2, CYP2C19, CYP2C9, CYP3A, CYP2C8, and CYP2D6. Rucaparib moderately inhibited UGT1A1. Rucaparib induced CYP1A2, and downregulated CYP2B6 and CYP3A4 at clinically relevant concentrations. Rucaparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and a potent inhibitor of multidrug and toxin extrusion transporters 1 and 2K, and a moderate inhibitor of organic cation transporter (OCT) 1, BCRP, and P-gp. CYP2D6, and to a lesser extent, CYP1A2 and CYP3A4, metabolise rucaparib. Rucaparib exposures were similar between extensive metabolizers and poor metabolisers of CYP2D6.

2 TRIAL DESIGN

Within the rucaparib subgroup, randomisation will be stratified via minimisation according to Section 3.7 of the main protocol, with the addition of rucaparib biomarker determination details (mutation only vs %LOH only vs mutation and %LOH).

*****PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL INCLUSION/EXCLUSION CRITERIA*****

2.1 Inclusion Criteria

1. Patients with urothelial cancer and either BRCA1 or BRCA2 (germline or somatic) mutation and/or high %LOH and/or mutation to a HRD associated gene (as defined by the ATLANTIS central laboratory) demonstrated through the centralised laboratory at pre-screening. Patients who are already known to have a somatic or germline mutation in either BRCA1 or BRCA2 established through an accredited laboratory may potentially be eligible without the result of central biomarker confirmation following agreement with the Chief Investigator or designee (central sample submission and screening consent is still required for confirmation although this will not override the positive local result).

2. Able to swallow study drug.

3. Adequate organ and marrow function with laboratory values as follows within 7 days before the first dose of rucaparib:

   l. ANC ≥1.5 x 10^9/L (without colony stimulating factor support);
   m. Platelets ≥100 x 10^9/L;
   n. Hemoglobin ≥ 9 g/dL;
   o. Bilirubin ≤ 1.5 × the ULN.
   p. ALT and AST ≤ 3.0 × ULN in the absence of or ≤ 5x ULN in the presence of liver metastases.
   q. Serum albumin ≥ 28 g/L;
   r. Creatinine clearance (CrCl) ≥ 30 mL/min, measured or estimated using the Cockcroft and Gault equation or Wright formula.

4. Sexually active patients (men and women) of reproductive potential and their partners of reproductive potential must use 2 highly effective methods of contraception during the course of the study and for at least 6 months following the last dose of rucaparib. Acceptable forms of contraception are described in section 9.3 of the main protocol.

2.2 Exclusion Criteria

1. Prior treatment with any PARP inhibitor.

2. Previous history of hypersensitivity to any active or inactive excipients of rucaparib.

3. Pre-existing duodenal stent and/or other gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with the absorption of rucaparib.

4. Previous history of myelodysplastic syndrome.

5. Evidence of significant uncontrolled concomitant illness that could affect compliance with the protocol or interpretation of study results.

6. Symptomatic and/or untreated central nervous system metastases.

7. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (e.g., warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel). Low-dose aspirin for cardioprotection (per local applicable guidelines) is permitted.

*****PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL INCLUSION/EXCLUSION CRITERIA*****

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria should be addressed via contact with the CTU prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply.

3 TRIAL PROCEDURES

Tumour samples will be sent to the ATLANTIS Central Laboratory at Barts Cancer Institute, through the same process described in section 4.1.1 of the main protocol. Samples for determination of HRD biomarker status in candidates for the rucaparib subgroup of ATLANTIS will then be sent to a collaborating laboratory where a genomic profile NGS assay will be applied within a CLIA certified laboratory. Most tumour samples would be anticipated to be adequate for testing for all current alternative ATLANTIS biomarkers. Where this is not the case, biomarker analysis will be prioritised based on current recruitment status to each drug subgroup.

3.1 Screening Procedures

There are no additional tests within 4 weeks of randomisation required over and above those listed in the main protocol.

The following is required within 7 days of randomisation in addition to those listed in the main protocol:

Serum cholesterol

The screening laboratory determinations can be used as week 1 pre-dose blood tests as long as they are not >7 days prior to first administration of trial treatment. If >7 days prior to first administration of trial treatment then the specified blood tests for week 1 should be repeated.

3.2 Procedures at each visit on rucaparib/placebo (see schedule of assessments table, page 2)

Additional tests required over and above those listed in the main protocol:

Serum cholesterol

3.3 Radiological Investigations Every 12 Weeks

There are no additional radiological investigations required over and above those listed in the main protocol.

3.4 End of Trial Procedures

There are no additional procedures required over and above those listed in the main protocol.

3.5 Follow-Up

There are no additional follow-up procedures required over and above those listed in the main protocol.

4 TREATMENTS

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

Control arm: Matched placebo 600mg twice daily and can be taken either with food or without food.

Experimental Arm: Rucaparib 600mg twice daily and can be taken either with food or without food.

4.1 Specific Drug Information

4.1.1 Rucaparib

Rucaparib and placebo are considered IMP for the purposes of this trial.

Rucaparib is supplied as 200mg or 250mg tablets or identical matched placebo. The dosage for the study is 600mg twice daily in nominally 28 day cycles. Tablets are provided in HDPE bottles, each containing 60 tablets. Patients will remain on continuous twice daily dosing until progression or unacceptable toxicity. Refer to Rucaparib Investigator Brochure for information regarding the physical and chemical properties of rucaparib and a list of excipients. Rucaparib and placebo should be stored between 15^{o}C and 30^{o}C.

4.1.1.1 Rucaparib/ Placebo Dispensing, Accountability and Administration

The investigator or a delegated individual (e.g. pharmacist) must ensure that the trial drugs are dispensed in accordance with the protocol, local Standard Operating Procedures and applicable regulatory requirements. Each prescription will cover one cycle (28 days) of rucaparib or placebo.

4.1.1.2 Rucaparib/ Placebo Dispensing and Accountability

Bottle number, batch number, dose prescribed, quantity and expiry of the drug supplied must be recorded in the accountability logs. Both bulk stock and individual patient accountability logs must be completed.

Patients will be required to return all bottles (including empty bottles) of trial medication at the next dispensing visit and again upon the completion of treatment. Any remaining tablets must be documented in the accountability logs. Any evidence of non-compliance with the prescribed dosing must be reported to the local PI. Any potential patient medication compliance issues should be addressed in a timely manner.

Full instructions regarding management, labelling and accountability of rucaparib/ placebo is given in the IMP Management and Accountability Document (Rucaparib) for the trial.

4.1.1.3 Rucaparib/ Placebo Administration

The start of rucaparib or placebo dosing should occur within 3 days after randomisation. Patients will take the rucaparib or placebo dose twice daily, self-administered at home at the same time each day, as close to 12 hours apart as possible. The assigned dose is 600mg rucaparib taken twice daily. A dose of 600mg should be maintained in the absence of treatment-emergent toxicity. Rucaparib or placebo can be taken either with food or without food and should be taken with a glass of room temperature water (approximately 240mls). The tablets should be swallowed whole without crushing or chewing.

Patients should be instructed to not make up vomited doses and to maintain the planned dosing schedule. Patients should not make up for missed doses if more than 4 hours have elapsed after the time the patient would usually take the dose. In the event of missed doses, patients should not take 2 doses to make up for the one missed.

4.1.1.4 Rucaparib/ Placebo Supplies

Rucaparib or identically matched placebo will be supplied free of charge by Clovis Oncology for use by patients in this trial and will be trial-specific investigational medicinal product trial stock. These will be shipped to site directly from Almac.

- Packaging, labelling and preparation of rucaparib and placebo will be performed in a way that will ensure blinding throughout the trial.

- Labelling of the rucaparib and placebo will be performed in accordance with Good Manufacturing Practice and in accordance with local labelling requirements. The labels will contain information to meet the applicable regulatory requirements.
- Only those supplies intended for use in the trial should be dispensed to the trial participants and clinical trial supplies must be dispensed in accordance with the trial protocol.
- Upon arrival of investigational product at site, site personnel should check the supplies for damage and verify proper identity, quantity and integrity of seals and report any deviations or product complaints to the CRUK Glasgow CTU upon discovery.
- All trial medications must be stored in a secure area with access limited to the investigator and authorised site staff and under physical conditions that are consistent with the specific requirements of the medication. For batch specific instructions and information on the shelf life see the packaging.
- Full instructions regarding management, labelling and accountability of rucaparib and placebo is given in a separate IMP Management and Accountability Document (Rucaparib) for the trial.

4.1.1.5 Duration of Treatment

See section 6.11.1 of the main protocol.

4.2 Non-IMPs

There are no non-IMPs in this subgroup treatment schedule.

4.3 Supportive Medications

- Antiemetics and antidiarrhoeal medications are allowed for treatment or prophylaxis according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, ASCO or ESMO guidelines).
- Drugs used to control bone loss (eg, bisphosphonates and denosumab) can be continued if started before randomization and the benefit outweighs the risk per the investigator's discretion (Note: After randomization, the use of these drugs requires Sponsor approval with the exception of management of disease related hypercalcemia in emergency situations. However, this should subsequently be reported to the Sponsor for acknowledgement and post-initiation approval).

- Transfusions, hormone replacement, and short term higher doses of corticosteroids (above the physiologic replacement dose) should be utilized as indicated by standard clinical practice.
- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively.

4.4 Concomitant Therapy

PLEASE REFER TO MAIN BODY OF PROTOCOL FOR INFORMATION ON CONCOMITANT THERAPY

4.5 Prohibited Therapy

Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct Factor Xa inhibitors), or antiplatelet inhibitors such as clopidogrel is not permitted.

PLEASE REFER TO MAIN BODY OF PROTOCOL FOR INFORMATION ON PROHIBITED THERAPY

4.6 Interactions with other medications

Based on in vitro CYP interaction studies, caution should be exercised for concomitant medications with narrow therapeutic windows that are substrates of CYP2C9 e.g. celecoxib and/or CYP3A e.g. warfarin (prohibited, see section 4.5), phenytoin, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine, avanafil, buspirone, darifenacin, darunavir, everolimus, ibrutinib, lomitapide, midazolam, naloxegol, saquinavir, simvastatin, tipranavir, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, sildenafil, ticagrelor, tolvaptan. Caution should also be exercised with CYP1A2 substrates, particularly those with a narrow therapeutic index (eg tizanidine, theophylline, duloxetine, caffeine, melatonin). Selection of an alternative concomitant medication is recommended where possible.

Caution should also be exercised for concomitant use of certain statin drugs (eg rosuvastatin and fluvastatin) due to potential risk in increased exposure from inhibition of BCRP and CYP2C9.

In vitro studies show that rucaparib is a potent inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could decrease renal elimination and liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib.

Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers. However, it should be noted that recent data showed that the risk of interaction of rucaparib with CYP34A perpetrators is largely diminished.

4.7 Dose Modifications for Treatment- Emergent Toxicity

Adverse events can occur early (within the first few weeks) of treatment with rucaparib eg. gastrointestinal disorders, fatigue, myelosuppression, dysgeusia and anorexia, and should be managed with best supportive care at the earliest signs of toxicity (if not addressed in toxicity specific guidance below). Substantial acute toxicities should be managed as medically indicated and with temporary suspension of rucaparib as appropriate. Dose modifications for toxicities are allowed as clinically indicated by the treating physician.

Management of treatment-emergent ALT/ AST elevations

Elevated ALT/ AST have been reported with rucaparib and should be monitored by measuring biochemistry results as per schedule of assessments (pages 4 - 5). Table 1.0 provides treatment guidelines for elevated ALT/ AST deemed by the investigator as likely to be related to rucaparib.

Table 1.0 Management of ALT/AST elevation related to rucaparib

Severity of ALT/AST Elevation	**Management guideline**
ALT or AST >20 x ULN	Hold rucaparib until values have returned to grade 2 or better. Resume rucaparib on a reduced dose (see section 4.7.1). Monitor ALT/ AST weekly for 3 weeks after rucaparib is restarted.

ALT or AST 5- 20 x ULN	Repeat liver function tests weekly until resolution to Grade 2. Continuation of rucaparib is permitted provided bilirubin is <ULN and Alkaline Phosphatase is <3 x ULN. If levels do not decline within 2 weeks or continue to rise, dose interruption (see section 4.7.1) and resolution to ≤ Grade 2 is required before restarting rucaparib at the current or a reduced dose.

Management of treatment-emergent cholesterol elevations

≥ Grade 3 (>10.34- 12.92 mmol/L) cholesterol elevations should be managed with dose interruption and/or dose reduction and concomitant treatment with a HMG-CoA reductase inhibitor. Caution should be noted for the use of certain statin drugs, see section 4.6 for further details.

Management of treatment-emergent myelosuppression

Grade 3/ 4 myelosuppressive events should be treated with best supportive care and dose interruption and/or dose reduction. Additional diagnostic evaluation, including bone marrow examination, should be considered for patients with persistent myelosuppression that does not stabilize or recover with rucaparib treatment modification.

Treatment may recommence if the following levels are met:

- ANC ≥ 1.0 x 10^9/L
- Platelet count ≥ 100 x 10^9/L

Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.

Additional details regarding toxicities and their management can be found in the Rucaparib IB.

4.7.1 Dose Reductions

Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

A maximum of two dose reductions are allowed, as per table 2.0 below:

Table 2.0 Dose Reductions

Dose level	Rucaparib/placebo dose	Re-escalation Details
Starting dose	600 mg twice daily	
First dose reduction	500 mg twice daily	Dose re-escalation is not permitted.
Second dose reduction	400 mg twice daily	

The dose may be reduced (to 500mg of rucaparib/placebo twice daily, with a possible second dose reduction to 400mg twice daily) due to treatment related toxicity at the discretion of the treating clinician. Patients with grade 3 or 4 toxicity (as per CTCAE version 4.03) should be considered for a dose reduction after temporary suspension, following recovery to grade 1 or baseline. Discussion with the Chief Investigators for dose reductions is advised but not mandated.

4.7.2 Dose Interruptions

Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities, and consideration should be given to a dose reduction as outlined in 4.7.1 when toxicity resolves to grade 1 or baseline.

Patients should have rucaparib interrupted immediately unless the following criteria are met:

- Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor.
- Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.

Patients may interrupt treatment for up to 28 days. Dose interruptions of >14 days should be reported to the Sponsor. Cessation of therapy for >28 days due to treatment related toxicity should result in permanent drug discontinuation. In the event of dose delays, radiological assessments should remain on schedule and be performed in line with the protocol schedule, regardless of the number of cycles of treatment received by the patient. Care should be taken to

record all dose modifications accurately.

4.7.3 Specific precautions

Pregnancy

Rucaparib has been shown in embryo-fetal development studies to be embryotoxic at all doses administered. In addition, there is the potential for PARP inhibitors to affect spermatogenesis. Monthly serum pregnancy testing is required for female patients on rucaparib and recommended for female partners of male patients of reproductive potential. Treatment should be discontinued immediately in any woman found to have a positive pregnancy test while taking rucaparib.

All study subjects of reproductive potential and their partners must use two highly effective medically accepted methods of contraception (see section 9.3 of main protocol) during the course of treatment with rucaparib and for at least 6 months following the last dose of rucaparib. Male patients must not make semen donations for 6 months following the last dose of rucaparib.

*****PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL INFORMATION ON PREGNANCY*****

Photosensitivity

Patients taking rucaparib should be advised to use typical precautions when going outside, such as applying sunscreen and/or covering exposed skin with clothing and wearing hat/sunglasses, as photosensitivity has been observed with the drug.

4.8 Emergency Unblinding

All Principal Investigators and/ or members of staff delegated to unblind patients will have access via the unblinding system that allows them to break the blind for an individual patient in an emergency situation as described above.

Site personnel will access the unblinding system via a secure website, using individual access codes. Trial specific user guides and PIN details will be sent to each site after initiation.

The telephone line for the unblinding system helpdesk is 0800 587 7844 or it can be contacted by email: gatewaysupport@almacgroup.com. Please note that the unblinding system helpdesk are only able to provide assistance with the function of the system, and this is service is provided Monday- Friday. Please state 'ATLANTIS-2 Unblinding System Issue' when contacting the helpdesk.

Each site must have arrangements in place to cover unblinding 24 hours each day.

4.9 Unblinding Following Final Analysis

All patients ongoing at the time of final analysis will be unblinded and informed in sufficient time for ongoing access arrangements to be made by the investigator, if considered in the patient's best interests. Trial IMP supply will stop completely once these arrangements are in place.

5 TRANSLATIONAL RESEARCH

An important exploratory objective in this group of patients will be to discover predictive nature of the positive HRD biomarker signature. Germ line material will be taken for SNP analysis and free circulating tumor DNA and plasma will be collected. Samples will be processed in accordance with the ATLANTIS lab manual.

6 SAFETY REPORTING

6.1 Recording of Adverse Events and Serious Adverse Events

In addition to details given in section 9.2.1.2 (Recording of Adverse Events) in the main body of the protocol, for patients receiving rucaparib, all AEs and SAEs must be recorded/reported from rucaparib subgroup consent and followed until resolution, or for 30 days after discontinuation of rucaparib treatment, whichever comes first, or until toxicity has resolved to baseline or ≤ grade 1, or until the toxicity is considered to be irreversible.

6.2 Serious Adverse Event Reporting for Adverse Events of Special Interest

In addition to the requirements for Serious Adverse Event (SAE) reporting provided in Section 9 (Safety Reporting) in the main body of the ATLANTIS protocol, Adverse Events of Special Interest (AESIs) must also be reported as SAEs whether thought to be related to rucaparib or not. AESIs include any non-serious and serious (meeting the main protocol definition of serious) instances of Myelodysplastic Syndrome (MDS), Acute Myeloid Leukaemia (AML), pneumonitis, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotising, alveolitis, hypersensitivity pneumonitis and organizing pneumonia. Such events must be reported within a maximum of 24 hours following first awareness, as SAEs "Considered medically significant by the Investigator". AESIs require to be reported up to 30 days after discontinuation of rucaparib, and any AESIs beyond this time only need reported if the Investigator considers the event related to rucaparib and meets the definition of seriousness, with the exception of MDS and AML. Any event

of MDS or AML must be reported as SAEs regardless of causality following permanent cessation of rucaparib until the end of the trial

6.3 Pregnancy – Duration of Contraception and Follow-Up for Pregnancy

In addition to the information provided in Section 9.3 (Pregnancy) in the main body of the ATLANTIS protocol and section 4.7.3 (Specific Precautions- Pregnancy) of the rucaparib-specific appendix, all advice regarding contraception and follow-up for pregnancy applies for 6 months following the last administration of rucaparib.

6.4 Reference Safety Information

The Investigator Brochure section 6 Reference Safety Information for rucaparib will act as the RSI for this subgroup of the trial.

7 STATISTICS AND DATA ANALYSIS

7.1 Trial Design and Sample Size

The general study design can be found in the main protocol section 11.1.

The trial design for the rucaparib arm assumes the following:

- That 25% of patients will be biomarker positive based on the analysis undertaken within the TCGA dataset.
- Of the 100 patients entering ATLANTIS every year, 21.25 will enter the rucaparib comparison arm allowing for competition with other ATLANTIS comparison arms.
- A median PFS in the control arm of 5.4 months.

A hazard ratio of 0.5 is targeted based on the striking effect seen with PARP inhibitors in a similar setting in ovarian cancer using a similar HRD biomarker signature for patient selection. This requires 39 PFS events which can be obtained by recruiting 48 patients over 27 months with 8 months subsequent follow-up. This number also provides >80% power (10% 1-sided) to detect a difference in the reduction in the size of measurable disease corresponding to a standardized effect size of 0.7. There will be a non-binding test for futility after half the PFS events have occurred (this will be after 37 patients have been recruited approximately).

7.2 Analysis Plan

As per section 11.2 of main protocol.

Due to early closure of the trial, analysis is planned to take place after 30 PFS events have been observed. This provides 85.4% power with 20% (one sided) alpha.

8 REGULATORY

8.1 Funding

This drug arm within the ATLANTIS umbrella trial structure is funded by an educational grant from Clovis Oncology. Please refer to the site agreement for full information on any per patient/site payments.

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24 APPENDIX VII - ENZALUTAMIDE

****PLEASE NOTE THAT ALL INFORMATION CONTAINED IN THIS APPENDIX IS *IN ADDITION* TO THAT CONTAINED IN THE MAIN BODY OF THE ATLANTIS PROTOCOL****

Trial Summary

Title:	**ATLANTIS-3 (Enzalutamide)**
Trial Drug:	Enzalutamide
Trial Drug Background:	Enzalutamide is a potent androgen receptor signalling inhibitor which is licensed for the treatment of metastatic castration resistant prostate cancer (mCRPC). Unlike the previous generation of AR antagonists (such as bicalutamide), enzalutamide has no known agonist activity and is known to be active in patients with prostate cancer who have previously failed conventional androgen deprivation therapy. In men with mCRPC, the drug is generally well tolerated with few significant toxicities even with prolonged duration of administration (1, 2). Previous in vivo and in vitro data suggest that AR is an anti-cancer target in UC (3-6). Unpublished data from a directly relevant tissue microarray (derived from the LAMB study) show 30% of urothelial tumours (male and female patients) over-express the AR (1-3+) where it is associated with a poor prognosis (Berney and Powles, personal communication).
Treatment:	Patients who express the Androgen Receptor (AR positive) will receive either enzalutamide 160mg or placebo PO OD, in a double blind manner (n=80). Treatment will continue until progression. Both dose reductions and treatment breaks for toxicity will be permitted (see section 4.7).
Duration:	80 patients recruited over 32 months with 6 months follow-up post recruitment end should provide the 72 PFS events required.

Flow chart

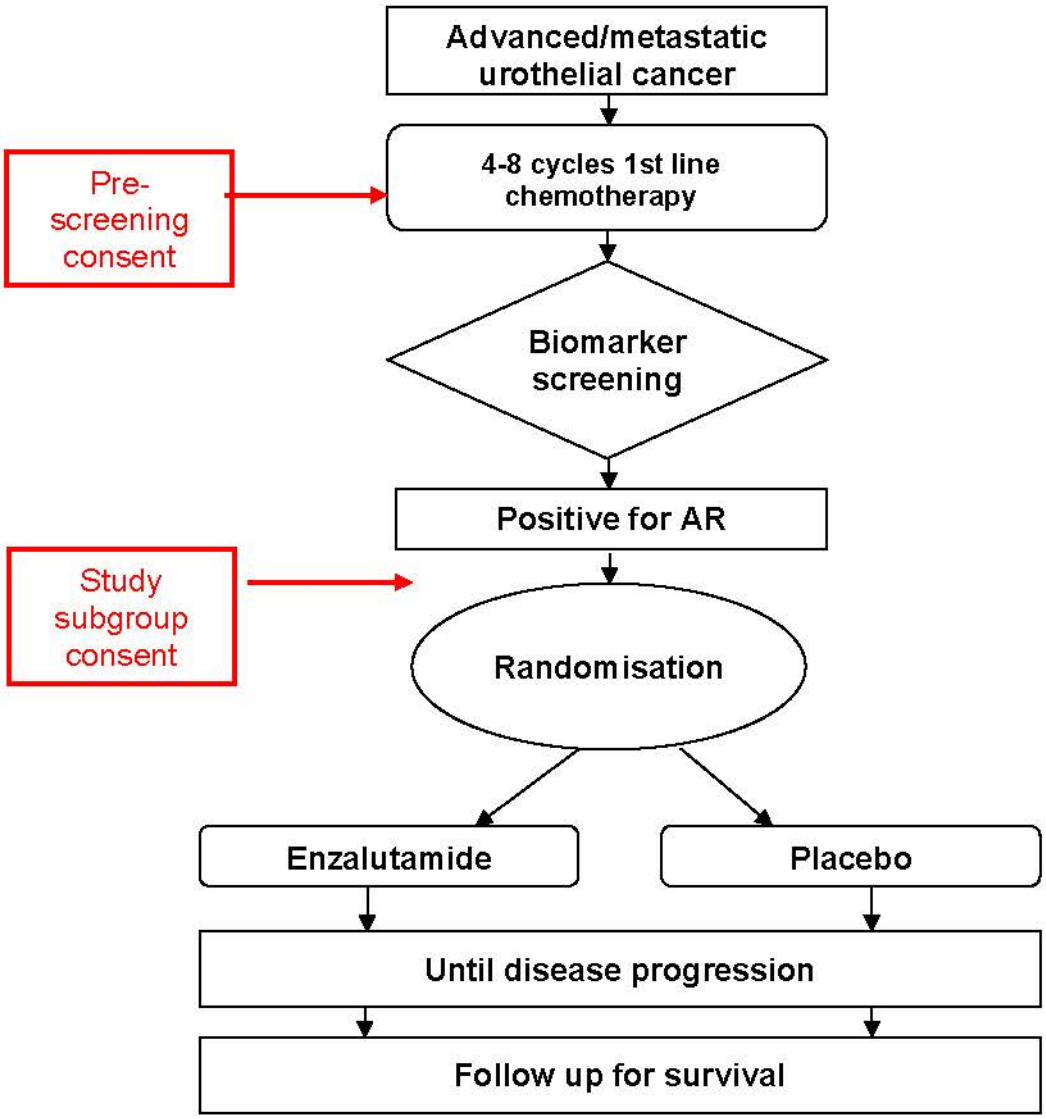

Figure 1: Enzalutamide flow chart

Schedule of Assessments – Enzalutamide/placebo subgroup

Procedure/ Assessment	Pre-Screen	Screening		Study treatment (4 weekly intervals)														Follow-up	
		≤4 weeks	≤1 week	Week 1	Week 5	Week 9	Week13	Week 17	Week 21	Week 25	Week 29	Week 33	Week 37	Week 41	Week 45	Week 49	Week 53+[17]	End of Treatment[12]	Off study treatment until progression[11]
Trial Procedures																			
Informed consent	X[1]	X[2]																	
Randomisation to subgroup			X																
Review of Eligibility Criteria		X																	
Demographic details	X[3]																		
Tumour characteristics and previous therapies	X[3]	X																	
Medical history		X																	
Physical examination[13]		X																X	
Smoking History		X																	
ECOG performance status	X[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[5]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[6]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG (12-lead)[14]		X																	
Toxicity/symptoms/ adverse events assessment	X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments																			
Full blood count	X[3]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	

Serum biochemistry	X[3]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	
Translational blood sample	X				X[4]													X[4]	
Estimated GFR	X[3]		X[7]																
Tumour specimen sent for central analysis [4]	X																		
Radiological Assessments																			
CT scan of chest, abdomen, pelvis		X[8]					X[8]			X[8]			X[8]			X[8]		X	X[10]
Treatment																			
Enzalutamide/placebo treatment[15]				X[16]	X	X	X	X	X	X	X	X	X	X	X	X	X		

This schedule demonstrates the appointments/procedures for the enzalutamide/placebo group ONLY. Please refer to individual IMP appendices for specific schedules and other visits for other treatments groups within the ATLANTIS trial.

[1]Patients should have signed and dated informed consent for pre-screening.

[2]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.

[3]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.

[4]Tumour samples and all other translational samples should be sent for the attention of Sakunthala Kudahetti, Barts Cancer Institute 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.

[5]Weight, height, pulse and blood pressure

[6]Human chorionic gonadotropin (HCG) results must be obtained and reviewed before the first dose of IMP is administered for women of child bearing potential.

[7]Haematology including full blood count with WBC, ANC (absolute neutrophil count), platelet count and haemoglobin. Biochemistry including sodium, potassium, AST/ALT, alkaline phosphatase (AP), LDH, bilirubin, creatinine, protein and albumin.

[8]All patients should have abdominal and pelvic CT or MRI, plus CT scan of the thorax. Patients should have baseline scanning then every 12 weeks until week 49 (+/- 2 weeks), then every 16 weeks (+/- 2 weeks) to week 97 then every 24 weeks (+/- 2 weeks) during trial treatment or after completion of treatment if terminated prior to disease progression, until closure of this individual drug subgroup.

(9)Patients who come off the trial should have tumour assessments within 4 weeks of coming off enzalutamide/placebo, irrespective of whether or not the patient is still being followed up for progression.

(10)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, 16-weekly or 24-weekly intervals as previously, until closure of this individual drug subgroup.

(11)Follow-up visits after progression will continue at the investigators discretion until death, until closure of this individual drug subgroup. Future treatment and cause of death must be recorded on the CRF.

(12)Must be performed within 4 weeks of stopping trial treatment.

(13)Physical examination should be performed during the screening visit (within 4 weeks prior to randomisation) and at the end of treatment visit. Additional physical examinations are only required as clinically indicated.

(14)Patients should have ECG at screening and then only repeated during treatment as clinically indicated.

(15)Enzalutamide or placebo dispensed every 28 days (28 day treatment cycle).

(16)Enzalutamide or placebo dosing must start within 3 days after randomisation.

(17)Continues every 4 weeks whilst on treatment.

1 INTRODUCTION

1.1 Background

1.1.1 Rationale

The purpose of this subgroup of the ATLANTIS trial is to test if Androgen Receptor (AR) inhibition can improve progression free survival (compared to placebo) in biomarker selected patients with advanced or metastatic bladder cancer who have recently completed first line chemotherapy.

Enzalutamide is a potent androgen receptor signalling inhibitor which is licensed for the treatment of metastatic castration resistant prostate cancer (mCRPC). Unlike the previous generation of AR antagonists (such as bicalutamide), enzalutamide has no known agonist activity and is known to be active in patients with prostate cancer who have previously failed conventional androgen deprivation therapy. In men with mCRPC, the drug is generally well tolerated with few significant toxicities even with prolonged duration of administration (1, 2).

Previous in vivo and in vitro data suggest that AR is an anti-cancer target in urothelial cancer (UC) (3-6). Unpublished data from a directly relevant tissue microarray (derived from the LAMB study) show 30% of urothelial tumours (male and female patients) over-express the AR (1-3+) where it is associated with a poor prognosis (Berney and Powles, personal communication).

2 TRIAL DESIGN

*****PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL INCLUSION/EXCLUSION CRITERIA*****

2.1 Inclusion Criteria

1. AR positive urothelial cancer as demonstrated by immunohistochemistry performed at the central laboratory.
2. Able to swallow study drug.
3. ANC ≥1.5 x 10^9/L
4. Platelets ≥100 x 10^9/L
5. Haemoglobin ≥9g/dL

6. Creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 30ml/min (by Cockcroft and Gault formula or Wright formula).
   Cockcroft and Gault equation
   i. Male: CrCl (mL/min) = 1.23 x(140 - age) × weight (Kg) / (serum creatinine umol/L);
   ii. Female: 1.04 x(140 - age) x weight (Kg)/ (serum creatinine umol/L)

   Wright formula - Without CK using Jaffe serum creatinine
   Estimated GFR (ml/min)= {[6580 – (38.8 x age)] x BSA x [1- (0.168 x sex)]} serum creatinine umol/L (where sex: male= 0 and female= 1, body surface area (BSA): Du Bois)
7. Bilirubin < 2.5 x ULN (unless documented Gilbert's syndrome)
8. AST or ALT < 5 x ULN.
9. Sexually active subjects (men and women) must use 2 highly effective methods of contraception during the course of the study and for 3 months after the last dose of enzalutamide. Acceptable forms of contraception are described in section 9.3 of the main protocol.

2.2 Exclusion Criteria

1. Prior history of hypersensitivity reaction to enzalutamide or any of its excipients.
2. Patients with hereditary problems of fructose intolerance.
3. Known brain or leptomeningeal metastases.
4. History of seizure or a condition which predisposes to seizure (e.g. severe head injury or stroke).
5. Active condition which affects drug absorption (e.g. prior gastrectomy or active peptic ulcer disease).
6. Myocardial infarction in last 6 months, unstable angina in last 3 months.
7. History of NYHA congestive heart failure grade III or IV, unless left ventricular ejection fraction ≥ 45%. Mobitz type II or type III heart block without pacemaker. History of clinically significant ventricular tachyarrhythmia (ventricular tachycardia, ventricular fibrillation, torsade de pointes). History of QT prolongation or risk factors for QT prolongation (e.g congenital long QT syndrome, uncontrollable/ recurrent hypokalaemia, family history of long QT syndrome or unexplained sudden death under 40 years of age).
8. Bradycardia (heart rate < 40bpm) at screening visit.
9. Uncontrolled hypertension (persistent systolic bp > 170mmHg or diastolic bp > 105mmHg).

10. Patients who are unable to stop treatment with prohibited concomitant medications as detailed in Section 4.5.

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria should be addressed via contact with the CTU prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply.

3 TRIAL PROCEDURES

Tumour samples will be sent to the ATLANTIS Central Laboratory at Barts Cancer Institute, through the same process described in section 4.1.1 of the main protocol. Most tumour samples would be anticipated to be adequate for testing for all current alternative ATLANTIS biomarkers. Where this is not the case, biomarker analysis will be prioritised based on current recruitment status to each drug subgroup.

3.1 Screening Procedures

There are no additional screening procedures required over and above those listed in the main protocol.

The screening laboratory determinations can be used as week 1 pre-dose blood tests as long as they are not >7 days prior to first administration of trial treatment. If >7 days prior to first administration of trial treatment then the specified blood tests for week 1 should be repeated.

3.2 Procedures at each visit on trial drug/placebo (see schedule of assessments table, page 5)

Additional tests required over and above those listed in the main protocol:

Pregnancy test (for female patients of child bearing potential only)

3.3 Radiological Investigations Every 12 Weeks

There are no additional imaging tests required over and above those listed in the main protocol.

3.4 End of Trial Procedures

There are no additional procedures required over and above those listed in the main protocol.

3.5 Follow-Up

There are no additional procedures required over and above those listed in the main protocol.

4 TREATMENTS

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

Control arm: Matched placebo 160mg (4x40mg) once daily.
Experimental Arm: Enzalutamide 160mg (4x40mg) once daily.

4.1 Specific Drug Information

4.1.1 Enzalutamide/ Placebo

Enzalutamide and placebo are considered IMP for the purposes of this trial.

Enzalutamide is supplied as soft capsules at the dosage strength of 40mg or identical matched placebo. Capsules are packed in high density polyethylene bottles with standard screw neck closures which are child resistant and tamper evident. Each bottle contains 124 capsules. Refer to Summary of Product Characteristics (SmPc) for information regarding the physical and chemical properties of enzalutamide and a list of excipients. Enzalutamide or placebo should be stored at controlled room temperature between 20- 25˚C, with excursions permitted between 15- 30˚C.

4.1.1.1 Enzalutamide/ Placebo Dispensing, Accountability and Administration

The investigator or a delegated individual (e.g. pharmacist) must ensure that the trial drugs are dispensed in accordance with the protocol, local Standard Operating Procedures and applicable regulatory requirements. Each prescription will cover one cycle (28 days) of enzalutamide or placebo.

4.1.1.2 Enzalutamide/Placebo Dispensing and Accountability

Bottle number, batch number, dose prescribed, quantity and expiry of the drug supplied must be recorded in the accountability logs. Both bulk stock and individual patient accountability logs must be completed.

Patients will be required to return all bottles (including empty bottles) of trial medication at the next dispensing visit and again upon the completion of treatment. Any remaining capsules must be documented in the accountability logs. Any evidence of non-compliance with the prescribed dosing must be reported to the local PI. Any potential patient medication compliance issues should be addressed in a timely manner.

Full instructions regarding management, labelling and accountability of enzalutamide/placebo is given in the IMP Management and Accountability Document (Enzalutamide) for the trial.

4.1.1.3 Enzalutamide/Placebo Administration

The start of enzalutamide or placebo dosing should occur within 3 days after randomisation. Patients will take the enzalutamide or placebo capsules once daily, preferably at bedtime. Doses will be self-administered at home. A dose of 160mg should be maintained in the absence of treatment-emergent toxicity.

The patient should take enzalutamide or placebo at approximately the same time every day. The capsules should be swallowed whole with water and not dissolved, chewed or opened. They can be taken with food or without food. The capsules should not be handled by women who are, or may become pregnant.

Patients should be instructed to not make up vomited doses and to maintain the planned dosing schedule. Patients should not make up for missed doses if more than 12 hours have elapsed after the time the patient would usually take enzalutamide or placebo. In the event of missed doses, patients should not take 2 doses to make up for the one missed.

4.1.1.4 Enzalutamide/Placebo Supplies

Enzalutamide or identically matched placebo will be supplied free of charge by Astellas Pharma for use by patients in this trial and will be trial-specific investigational medicinal product trial stock. These will be shipped to site directly from Sharp Clinical, England.

- Packaging, labelling and preparation of enzalutamide and placebo will be performed in a way that will ensure blinding throughout the trial.
- Labelling of the enzalutamide and placebo will be performed in accordance with Good Manufacturing Practice and in accordance with local labelling requirements. The labels will contain information to meet the applicable regulatory requirements.
- Only those supplies intended for use in the trial should be dispensed to the trial participants and clinical trial supplies must be dispensed in accordance with the trial protocol.
- Upon arrival of investigational product at site, site personnel should check the supplies for damage and verify proper identity, quantity, integrity of seals and temperature conditions and report any deviations or product complaints to the CRUK Glasgow CTU upon discovery.
- All trial medications must be stored in a secure area with access limited to the investigator and authorised site staff and under physical conditions that are consistent with the specific requirements of the medication. For batch specific instructions and information on the shelf life see the packaging.
- Full instructions regarding management, labelling and accountability of enzalutamide/placebo is given in a separate IMP Management and Accountability Document (Enzalutamide) for the trial.

4.1.1.5 Duration of treatment

See section 6.11.1 of the main protocol.

4.2 Non-IMPs

There are no non-IMPs in this subgroup treatment schedule.

4.3 Supportive Medications

There are no routinely indicated supportive medications with enzalutamide.

4.4 Concomitant Therapy

*****PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL CONCOMITANT THERAPY*****

4.5 Prohibited Therapy

Strong inhibitors of CYP2C8, including, but not limited to, gemfibrozil are prohibited as these may lead to an increased exposure to enzalutamide.

*****PLEASE REFER TO MAIN BODY OF PROTOCOL FOR ADDITIONAL PROHIBITED THERAPY*****

4.6 Interactions with other medications

Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters and may lead to loss of efficacy of other medicines.

Use with caution, substitute where possible:

Substrates for CYP3A4 with narrow therapeutic range (enzalutamide is an enzyme inducer) including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus.

Groups of medicinal products that can also be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, tramadol)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. acenocoumarol, warfarin, clopidogrel)
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Betablockers (e.g. bisoprolol, propanolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- Corticosteroids (e.g. dexamethasone, prednisolone)
- HIV antivirals (e.g. indinavir, ritonavir)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressant (e.g. tacrolimus)
- Proton pump inhibitor (e.g. omeprazole)
- Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)

- Thyroid agents (e.g. levothyroxine)

Patients taking medicines that are substrates of CYP2B6, CYP3A4, CYP2C19 or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects where active metabolites are formed) during the first month of enzalutamide treatment and their medicines dose adjusted where appropriate.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided if possible. If co-administration is deemed necessary by the treating-clinician, INR should be closely monitored as per local policy.

Drugs with a narrow therapeutic range that are substrates for P-gp (enzalutamide is a P-gp inhibitor) including but not limited to colchicine, dabigatran etexilate, digoxin, should be used with caution. Theoretically, induction or inhibition of BCRP, MRP2, OAT3 and OCT1 substrates cannot be excluded and medicines which are substrates for these transporters should be used cautiously.

The concomitant use of enzalutamide with medicines known to prolong the QT interval or have the ability to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin or antipsychotics should be carefully evaluated. The list of drugs which are known to prolong or may prolong the QT interval is constantly being updated. Please consult crediblemeds.org for the most up to date list.

Please note, the above lists of concomitant medicines to be used with caution is not exhaustive and reference to the SmPC should always be made.

4.7 Dose Modifications for treatment-emergent toxicity

Some adverse events can occur early (within the first few weeks) of treatment with enzalutamide eg. hot flushes and fatigue, and should be managed with best supportive care at the earliest signs of toxicity. Substantial acute toxicities should be managed as medically indicated and with temporary suspension of enzalutamide/ placebo as appropriate. Dose modifications for toxicities are allowed as clinically indicated by the treating physician.

Enzalutamide therapy should be discontinued for the following adverse events and should be discussed with Chief Investigator prior to re-commencing therapy:

Seizures – Any patient suffering a seizure after commencing enzalutamide/placebo should have immediate discontinuation of trial therapy and discussion with the Chief Investigator (or delegated representative) prior to re-commencing study therapy. All patients should be treated as per local guidelines for seizures, referral to a neurologist is recommended but not mandated.

Posterior Reversible Encephalopathy Syndrome (PRES) – There have been rare reports of PRES in patients receiving enzalutamide. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual or neurological deficits, with or without hypertension. Patients diagnosed with PRES should immediately discontinue enzalutamide/placebo and must be discussed with the Chief Investigator (or delegated representative) prior to recommencing study therapy.

4.7.1 Dose Reductions

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 is attributed to the study drug and cannot be ameliorated by the use of appropriate medical intervention, given at the discretion of the investigator, may interrupt study drug until the toxicity grade improves to grade 2 or lower (see section 4.2 if toxicity resolves to a tolerable grade 2). Subsequent, study drug dosing may be restarted at the original dose (160mg) or a reduced dose of 80mg/day.

A maximum of one dose reduction is allowed, as per table 4.1 below:

Table 4.1 Dose Reductions

Starting dose	160 mg/day (4 capsules)	Dose re-escalation is not permitted.
First dose reduction	80 mg/day (2 capsules)	

4.7.2 Dose Interruptions

Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities, and consideration should be given to a dose reduction as outlined in 4.7 and 4.7.1 when toxicity resolves to grade 1 or baseline. Patients in whom toxicity resolves to tolerable grade 2 may recommence enzalutamide/placebo if they are deriving clear clinical benefit, as determined by the investigator and agreed by the CI(s).

Patients should have enzalutamide/placebo interrupted immediately unless the following criteria are met:

- Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor.
- Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.

Patients may have their treatment interrupted for up to 28 days. Dose interruptions of >14 days should be reported to the Sponsor. Cessation of therapy for >28 days due to treatment related toxicity should result in permanent drug discontinuation. If the patient is to undergo planned surgery, including dental surgery, during the trial, and enzalutamide/placebo is anticipated to be interrupted for > 28 days this must be discussed first with the Chief Investigator or delegate prior to entry into the main study. In the event of dose delays, radiological assessments should remain on schedule and be performed in line with the protocol schedule, regardless of the number of cycles of treatment received by the patient. Care should be taken to record all dose modifications accurately.

4.8 Emergency Unblinding

All Principal Investigators, and/or members of staff delegated to unblind patients will have access via the unblinding system that allows them to break the blind for an individual patient in an emergency situation as described above.

Site personnel will access the unblinding system via a secure website, using individual access codes. Full telephone support is available via a toll free telephone number. Trial specific user guides and PIN details will be sent to each site after initiation.

The toll free access line for the unblinding system helpdesk is 0141 330 4744. Please note that the unblinding system helpdesk are only able to provide assistance with the function of the system, and this is service is provided Monday- Friday 9am- 5pm. Please state 'ATLANTIS-3 Unblinding System Issue' when contacting the helpdesk. Each site must have arrangements in place to cover unblinding 24 hours each day.

4.9 Unblinding Following Final Analysis

All patients ongoing at the time of final analysis will be unblinded and informed in sufficient time for ongoing access arrangements to be made by the investigator, if considered in the patient's best interests. Trial IMP supply will stop completely once these arrangements are in place.

5 TRANSLATIONAL RESEARCH

There is no additional translational research associated with this treatment subgroup in addition to the main protocol.

6 SAFETY REPORTING

6.1 Recording of Adverse Events and Serious Adverse Events

In addition to details given in section 9.2.1.2 (Recording of Adverse Events) in the main body of the protocol, for patients receiving enzalutamide, all AEs and SAEs must be recorded/reported from enzalutamide subgroup consent and followed until resolution, or for 30 days after discontinuation of enzalutamide treatment, whichever comes first, or until toxicity has resolved to baseline or ≤ grade 1, or until the toxicity is considered to be irreversible.

6.2 Pregnancy – Duration of Contraception and Follow-Up for Pregnancy

In addition to the information provided in Section 9.3 (Pregnancy) in the main body of this protocol, all advice regarding contraception and follow-up for pregnancy applies for 3 months following the last administration of enzalutamide.

6.3 Reference Safety Information (RSI)

Section 4.8 "Undesirable Effects" of the SmPC produced by Astellas Pharma for enzalutamide will act as the RSI for this subgroup of the trial.

7 STATISTICS AND DATA ANALYSIS

7.1 Trial Design and Sample Size

The general study design can be found in the main protocol section 11.1.

For this component patients will be randomized between enzalutamide or placebo (1:1). The median PFS on the placebo arm is estimated to be 4 months. The comparison between the arms is designed to detect an improvement to the median PFS of 6.7 months with enzalutamide (this corresponds to a hazard ratio of 0.6; the size of difference is appropriate for a targeted agent in the target population). This requires 72 PFS events. Assuming a recruitment rate of 30 patients per year, 80 patients recruited over 32 months with 6 months follow up post recruitment end should provide this number of events.

This number also provides 90% power (10% 1 sided) to detect between the arms a difference in the reduction in size of measurable disease corresponding to a standardised effect size of 0.65.

7.2 Analysis Plan

As per section 11.2 of main protocol.

Due to early closure of the trial, 72 PFS events will not be reached. Analysis will take place once adequate follow-up and data cleaning has been performed. No statistical re-calculations have been performed due to the small number of patients recruited and analyses will be mostly descriptive.

8 REGULATORY

8.1 Funding

This drug arm within the ATLANTIS umbrella trial structure is funded by an educational grant from Astellas Pharma Europe Ltd. Please refer to the site agreement for full information on any per patient/site payments.

9 REFERENCES

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