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

We would like to thank the participants and their families that took part in this research and also thank all study investigators and staff from participating hospitals, the study team and study co-sponsors.

The study was co-sponsored by the University of Glasgow and NHS Greater Glasgow & Clyde. Funding was received from Exelixis, Clovis Oncology, Astellas Pharma Europe, and Cancer Research UK.

The Chief Investigators were Professor Rob Jones, Professor of Oncology at the Beatson West of Scotland Cancer Centre, and Professor Tom Powles, Professor of Urology Cancer at St Bartholomew's Hospital.

Competing interests declared by some investigators include receipt of honoraria, research funding or expenses from pharmaceutical companies and investigators performing a consulting or advisory role to pharmaceutical companies.

People with lived experience of bladder cancer, through the charity Fight Bladder Cancer, were members of our Trial Management Group throughout the course of the trial. They participated in study design and development, reviewed documents that were to be given to patients to ensure they were clear and informative, and contributed to decisions about how the study was run and how results would be shared.

The study took place at 34 hospitals across the UK, between February 2017 and March 2023.

Background

Urothelial cancer (UC, cancer of the bladder and associated structures) affects around 20,000 people a year in the UK and can be difficult to treat once it has spread. Chemotherapy is the standard treatment for people with metastatic UC (MUC, cancer which has spread to other parts), aiming to control the tumour and maintain a good quality of life for as long as possible. It often works at first, but for many people the cancer starts growing again within months (usually within 6 months of completion of treatment). The outcome, once relapse has occurred, is very poor (average overall survival is 8 months). The aim of ATLANTIS was to investigate whether giving drugs after chemotherapy delays further growth of the cancer, and to help develop specific treatments for specific subtypes of urothelial cancer.

The trial investigated whether targeted therapy after chemotherapy, with treatment selection based on biomarker expression (molecules present in tumour tissue), delayed time to disease getting worse and improved overall survival. In simple terms, the study asked whether matching treatments to features of a person's tumour could keep the cancer under control for longer.

Trial Treatment

Patients with previously diagnosed locally advanced and/or metastatic, inoperable urothelial cancer, who had previously received at least 4 cycles of first-line chemotherapy were allocated into one of three different treatment subgroups based on biomarker analysis on their tumour tissue. A sample from the tissue used to diagnose their cancer was sent to a central laboratory for testing, looking for relevant molecules to determine which of the active drug(s) their cancer may respond to best.

Patients were then screened and randomised to receive either active drug or placebo (dummy drug) within that subgroup. This was a random allocation, with roughly equal numbers of patients in each

group receiving active drug or placebo. None of the patients, their clinicians or the study team knew whether the patient was on active drug or placebo.

Patients took the drug continuously every day (orally, either once or twice a day) until either their cancer progressed, or they experienced unacceptable toxicity (side effects). They were monitored every 4 weeks for toxicity, and had CT scans every 12 weeks to monitor disease progression. Additional blood samples were taken from patients at 3 timepoints (before, during and after treatment) to be stored for future genetic research.

279 patients were registered for biomarker screening.
115 patients were randomised into a treatment subgroup based on their biomarker results:

- 61 received cabozantinib or placebo (40mg tablets taken once a day)
- 40 received rucaparib or placebo (600mg tablets taken twice a day)
- 14 received enzalutamide or placebo (160mg tablets taken once a day)

Side Effects

Cabozantinib: Most side effects were mild to moderate and were already known for this drug. Ten percent or more of patients experienced abdominal pain, anorexia, constipation, diarrhoea, dry mouth, dysgeusia (taste disorder), dyspnoea (shortness of breath), fatigue, gastroesophageal reflux disease, headache, hoarseness, hypertension (high blood pressure), hyperthyroidism (overactive thyroid), hypothyroidism (underactive thyroid), metabolism and nutrition disorders, mucositis (oral thrush), myalgia (muscle pain), nausea, peripheral sensory neuropathy (nerve damage in hands and feet), urinary tract infection, vascular disorders or vomiting.

Skin reactions were of particular interest in the cabozantinib group and 10% or more of patients experienced dry skin, erythroderma (inflammation, redness and scaling), nail discolouration, nail loss, nail ridging, pain in the skin, hand-foot syndrome (redness, swelling, pain, tingling and peeling of palms and soles), pruritis (itching), rash (often like acne, or like measles) or skin ulceration.

Rucaparib: Side effects were similar to those seen when this drug is used in other cancers. Ten percent or more of patients experienced anorexia, diarrhoea, fatigue, hypertension, nausea or rash.

Enzalutamide: Side effects were similar to those seen when this drug is used in other cancers. Ten percent or more of patients experienced abdominal pain, arthralgia (joint pain), diarrhoea, fatigue, hypertension or nausea.

Results

Unfortunately, the study finished early as it was not possible to recruit the target numbers into each study drug group in a timely manner (the COVID-19 pandemic halted recruitment for a few months, and sites were then slow to re-open due to staffing challenges, which impacted overall study recruitment). In addition, new standard treatment became available, and it was therefore unethical to continue to recruit patients to the trial. Despite this, study analysis plans were amended, and robust statistical analysis was carried out on data from each of the 3 drug subgroups.

Cabozantinib/placebo group: There was no difference in overall survival time between patients receiving active drug or placebo. Adverse events related to treatment were low grade, but the most frequent reactions (fatigue, hypertension, nausea and diarrhoea) were more common with active drug. Overall, cabozantinib was tolerable, with patients receiving active drug for an average of 13 months vs 10 months of placebo. Though tolerable, cabozantinib did not show a significant benefit compared to placebo. This showed that cabozantinib is unlikely to be helpful as maintenance treatment after chemotherapy in this cancer.

Rucaparib/placebo group: Patients receiving rucaparib active drug had a longer period of time before disease progression than patients on placebo. Treatment related adverse events were mostly low grade, but the most frequent reactions (fatigue, nausea and rash) were more common with active drug. Rucaparib was tolerable, with patients receiving active drug for an average of 10 months vs 6 months of placebo. Rucaparib extended the time to progression, and further investigation of the drug is warranted.

Enzalutamide/placebo group: There was no difference in time to progression or overall survival time between patients receiving active drug or placebo. Adverse events related to treatment were low grade and in keeping with previous experience with this drug. Overall, enzalutamide was tolerable, with patients receiving active drug for an average of 4 months vs 3 months of placebo. Though tolerable, enzalutamide did not show a significant benefit compared to placebo.

Benefits to Patients and Researchers

This trial showed no benefit from cabozantinib in this setting, and this knowledge was contributory to the early closure of a large phase III trial in the USA using this drug – thus helping to protect patients from side effects of an ineffective treatment. The positive findings associated with rucaparib were presented simultaneously with similar results from another trial of a different drug in its class (PARP inhibitor). At present, there is no clear plan as to how to confirm these findings, but researchers are still considering further trials of PARP inhibitors in urothelial cancer. Because only a small number of people joined the enzalutamide group, it is difficult to know whether the drug could help a wider population.

Even though the study closed early, ATLANTIS has provided important information for patients and researchers. The trial also delivered a collection of tissue from a large number of patients with this relatively rare stage of the disease, all of whom underwent panel genomic analysis. This collection of samples and data has formed a valuable and accessible data set to explore new ideas to help understand the biology of bladder cancer and how this may relate to new treatments in the future.

No new trials directly linked to ATLANTIS are planned at the moment, however, the samples and data collected remain available to researchers for future studies.

A plain-English summary of the study results will be published on the Cancer Research UK website: https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-more-treatment-after-chemotherapy-for-advanced-urinary-tract-cancer-urothelial-cancer

Information regarding the study is also available on the clinical trial register: https://www.isrctn.com/ISRCTN25859465