The ATLANTIS trial – Can we be more 'precise' in managing urothelial cancer?

Urothelial cancer, which includes cancers of the bladder, ureter, renal pelvis and urethra, is the 7th most common cancer diagnosed in the United Kingdom. Patients diagnosed with advanced or metastatic urothelial cancer have a life expectancy of approximately one year with platinum-based chemotherapy treatment. Although the majority of patients who receive chemotherapy initially benefit, relapse is almost inevitable and occurs, on average 6 months after completion of chemotherapy. Once cancer relapse has occurred, patient life expectancy and quality of life can be poor. Some patients may be suitable for second line chemotherapy or, increasingly, immunotherapy treatments, but the benefits of these are uncertain and there is still no consensus as to which treatment is most appropriate in the second-line setting.

Until very recently, clinical trials of second-line treatments have largely been unsuccessful. Even with the new immunotherapy drugs, such as pembrolizumab, nivolumab, atezolizumab, evalumab or durvalumab, it is clear that some patients derive little benefit. There is, therefore, an urgent need to improve treatments for patients with metastatic urothelial cancer following first line chemotherapy. One way of meeting this need may be to offer 'maintenance treatment' on completion of first line chemotherapy to avoid or delay future relapse.

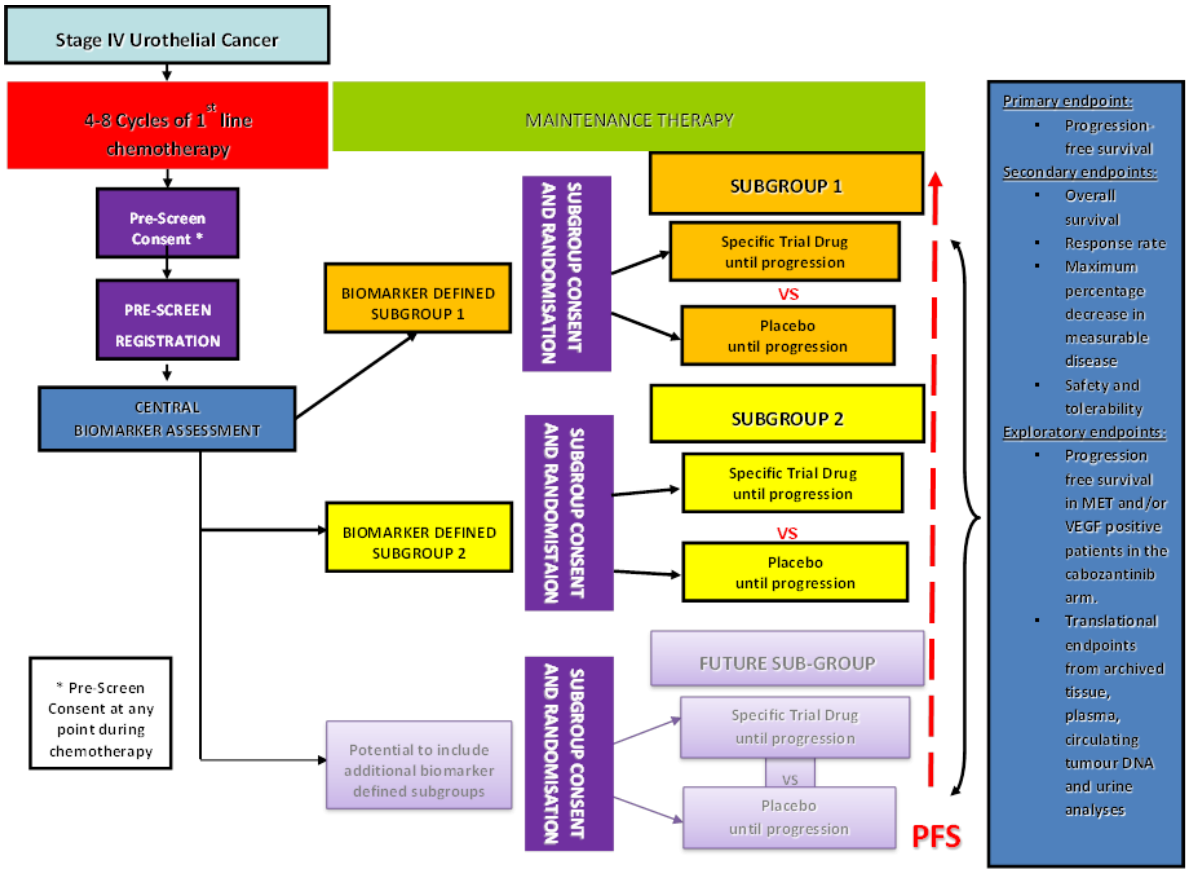
Urothelial cancers have been shown to display a number of 'biomarkers' (molecules that can be present or absent in an individual's cancer). These biomarkers can be used to identify subtypes or predict the behaviour of certain types of cancer, or possibly used as a 'target' against which specific treatments can be developed to treat cancer. This is known as a precision-medicine approach, where treatments are decided based on specific laboratory testing of an individual's cancer in order to try and determine the most effective treatment for that person.

ATLANTIS is a precision-medicine clinical trial for patients with metastatic urothelial cancer. The principle research question of the study is whether precision-medicine 'targeted' maintenance therapy after initial chemotherapy can delay the time until cancer relapse. Testing new treatments in combination with standard chemotherapy is difficult, as the side-effects of combining these can be very difficult for patients. Thus, using these treatments as maintenance therapy (the 'targeted' treatment commences at the end of first line chemotherapy) may be a more appropriate setting. This is the arena in which the ATLANTIS trial will introduce new precision-medicine treatments.

The ATLANTIS trial will be open to patients with metastatic urothelial cancer who have recently completed (or are currently going through) standard chemotherapy. The trial will be run at more than 20 centres in the UK. Patients who may be interested in the trial will be asked to consent to testing of their tumour, from tissue already stored in the local laboratory after their initial operation

or biopsy. This is called the pre-screening phase. The study doctor will arrange for this tumour sample to be sent to the ATLANTIS central laboratory for testing. The results should be available within 15 working days. If the pre-screening tests are positive or negative for the biomarkers being tested, patients may still be eligible to go into the main part of the ATLANTIS trial, where different treatments are being tested. The study flow chart is shown in *Figure 1*.

Figure 1. Study flow chart for the ATLANTIS clinical trial.



Within the study framework, patients whose tumour is not positive for any of the specific biomarkers being tested will be eligible for treatment in the group testing a new treatment called cabozantinib. Cabozantinib is a medication called a tyrosine kinase inhibitor and it is already in routine use in some patients with kidney or thyroid cancer. It works by targeting receptors present on cancer cells. Cabozantinib targets several different receptors, which in turn, may block tumour growth and angiogenesis (the development of a blood supply to the tumour). As the ATLANTIS trial progresses, further treatments will be added for patients whose tumour is positive for specific biomarkers.

Each of the treatments in ATLANTIS will be tested against the standard treatment for patients with metastatic urothelial cancer, which in this case is surveillance / monitoring without treatment. This is necessary to allow the study doctors to know whether the new form of 'maintenance' treatment is more effective than the conventional treatment. If patients and doctors were to know this from the outset, then it may affect how they participate in the trial. The study, therefore, also uses a placebo

with which to compare each treatment. This takes the form of a tablet that looks exactly like the medication being tested, but does not contain any active drug. Within the trial, half of patients will receive the active medication and the other half will receive placebo. Neither the study doctor nor patients will know which an individual receives.

ATLANTIS is not, of itself, a 'final test' of new treatment, but rather it is a way of testing multiple different drugs to try and find which ones work. It is likely that further testing will still be required for any drug which appears effective within the ATLANTIS trial. This is important, as it may be that effective drugs identified in ATLANTIS may be even more useful if given earlier in the course of the disease, for example before surgery ('neoadjuvant treatment'), where there is the possibility of increasing the number of patients who are eventually cured.

In Summary

The ATLANTIS trial is an exciting development in the treatment of patients with metastatic urothelial cancer. The study is the first of its kind in the UK facilitating an array of precision-medicine testing and hopefully a deeper understanding of how new treatments work for patients with metastatic urothelial cancer. If you feel you or someone else may be interested in participating in the ATLANTIS clinical trial, then ask your hospital specialist or contact the CRUK Clinical Trials Unit in Glasgow (http://www.crukctuglasgow.org/eng.php?pid=atlantis).

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