First results of the RE-AKT trial

RE-AKT Phase I cohort: A phase I dose-escalation study of enzalutamide in combination with the AKT inhibitor AZD5363 (capivasertib) in patients with metastatic castration resistant prostate cancer.

You previously agreed to take part in a clinical trial called RE-AKT, a study in advanced prostate cancer.

The main aim of the RE-AKT trial was to find out if a drug called Enzalutamide given in combination with a new drug called AZD5363 was safe for patients and to determine the optimum dose strength for a later study (the Phase II trial).

The other aim was to assess whether the drug combination could stop the cancer from progressing. Patients' response was measured by a decrease in PSA during treatment, a decrease in circulating tumour cells and by CT scans and bone scans. The research team were looking whether the prostate cancer was stable or there was a complete or partial response. Pharmacokinetics testing (a type of laboratory testing) was carried out to show if the two drugs when given together had the same activity as the activity seen when each drug is taken on its own.

Pharmacodynamics testing (another type of laboratory testing) was carried out to see if AZD5363 was able to block a specific pathway in cells which is known to promote cancer growth (the AKT pathway). Blood samples were taken to check for genetic markers that may affect the success of the treatment.

The results are now available and are described below.

Background:
Everybody who consented to take part in the RE-AKT Phase I trial was offered 1 week's treatment of AZD5363 alone. After this first week, AZD5363 was taken twice a day for 4 days with a 3 day break for a 28-day cycle. 160mg Enzalutamide was taken once a day on a continuous basis. The trial tested increasing doses of AZD5363 with a stable dose of Enzalutamide. Three doses of AZD5363 were tested, starting with 320mg, moving up to 480mg and finally back down to 400mg.

Data from the clinic appointments that you attended during the study have been collected and analysed at the Clinical Trial and Statistics Unit at The Institute of Cancer Research (ICR-CTSU). These results have been presented at an international conference and have been published in a leading medical journal so that doctors around the world can be made aware of the findings. You cannot be identified personally from any of the data used in any of the presentations or publications.

The early results were presented as a poster at the GU ASCO Conference, February 2017.
http://meetinglibrary.asco.org/content/179135-197

The full results publication is available at the following web address.
https://www.sciencedirect.com/science/article/pii/S0923753420360373

The results:

Participation in the study
16 men were recruited at the Royal Marsden Hospital from December 2014 to May 2016. 15 patients were well enough to receive treatment.

How well did the treatment work?
The RE-AKT trial met its main objective:

- For those patients on treatment where response could be measured at week 12,
  - 2 out of 10 patients (20%) showed a greater than 50% drop in their PSA result.
  - 1 out of 9 patients (11%) had either a partial response to treatment or stable disease.
  - 3 out of 7 patients (43%) had a drop in their circulating tumour cells in the blood.
  - The other patients had either stopped treatment at this time point or the results were not available.
  - Patients who had responded to treatment had either PTEN loss, or a AKT mutation, or had low or no AR-V7 expression in their tumour.

- The pharmacodynamic activity showed that the AKT pathway was blocked and therefore the drug combination was effective at each AZD5363 dose strength.
- The pharmacokinetic samples showed that there was an interaction between the Enzalutamide and AZD5363, which reduced the AZD5363 drug activity. This interaction did not affect the drug blocking the AKT pathway.

Did the treatments have side effects?

- Patients on the higher dose strength of 480mg AZD5363 with Enzalutamide were more likely to have a skin rash that covered the whole body.
- Other side effects such as diarrhoea, high glucose levels, loss of appetite and nausea were generally mild and manageable with supportive care.

What do these results mean?
The trial achieved its main objective and concluded that 400mg AZD5363 (given 4 days on and 3 days off) in combination with 160mg Enzalutamide was a safe and effective dose for larger Phase II trials.

Patients on this trial will have previously had other androgen receptor drug treatments, e.g. Abiraterone, which they have become resistant to. The results of this trial showed that AZD5363 may overcome this drug resistance.

Patients who showed response to treatment were found to have genetic changes in the PI3K/AKT/mTOR pathways in their tumour.

We would like to thank you for taking part in the RE-AKT Phase I trial. Without the contribution of people like you, this study would not have been possible.

If you have any questions about these results, please discuss them with your consultant.

The RE-AKT trial was funded by Astra Zeneca who supplied the AZD5363 free of charge. It was also supported by Astellas Inc who provided the Enzalutamide free of charge. The trial was endorsed by Cancer Research UK.

The Chief Investigator is Professor Johann de Bono from the Royal Marsden Hospital, Sutton. The RE-AKT trial is coordinated by the Clinical Trial and Statistics Unit at the Institute of Cancer Research (ICR-CTSU).