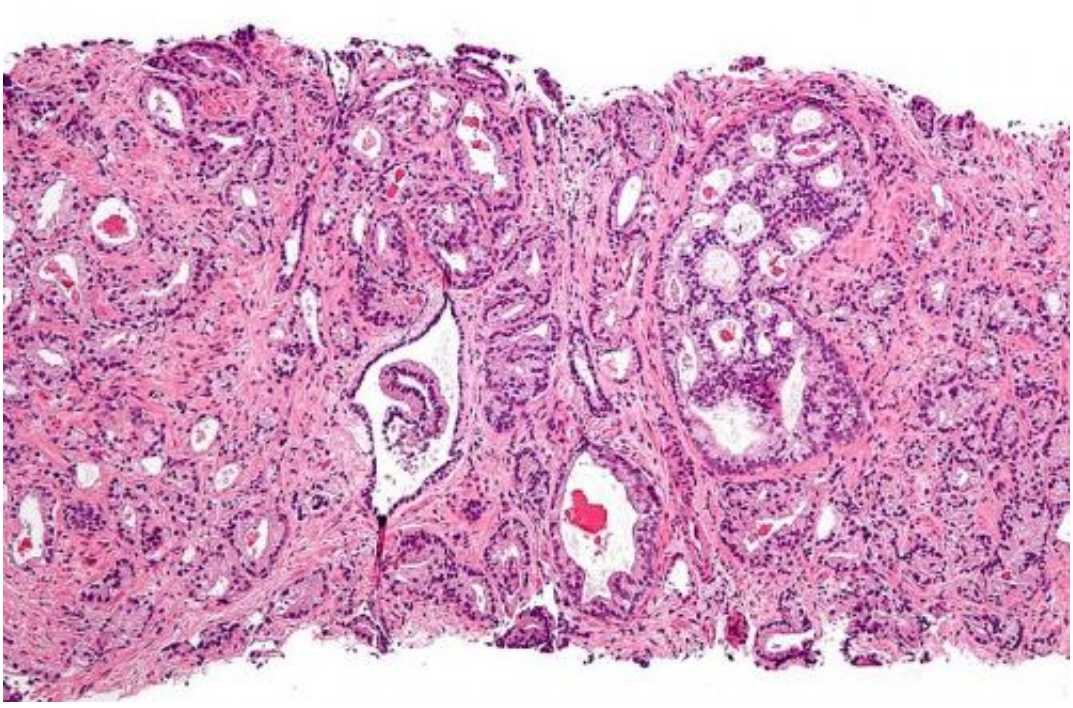
Landmark clinical trial shows gene-targeted drug can treat prostate cancer

October 28 2015



Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

A pioneering drug developed to treat women with inherited cancers can also benefit men with advanced prostate cancer, a major new clinical trial concludes.

The trial is a milestone in cancer treatment as the first to show the benefits of 'precision medicine' in prostate cancer - with treatment

matched to the particular genetic characteristics of a man's tumour.

Olaparib, the world's first drug to reach the market targeted against inherited cancer mutations, was found to benefit as many as a third of patients with prostate cancer, including many who did not inherit cancer genes but whose tumours had acquired defects in DNA repair.

An international consortium of researchers, led by experts at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, publish the trial's findings in the *New England Journal of Medicine* today.

The trial, called TOPARP-A, received support from a wide range of funders including Cancer Research UK, the Prostate Cancer Foundation, Stand Up To Cancer, Prostate Cancer UK and the Movember Foundation.

There was also support from the Investigator-Sponsored Study Collaboration between AstraZeneca and The NIHR Biomedical Research Centre at The Royal Marsden and the ICR, the NIHR Cancer Research Network, and Experimental Cancer Medicine Centre (ECMC) funding to the ICR and Royal Marsden, and several other ECMC sites.

In the trial, 49 men with treatment-resistant, advanced prostate cancer received olaparib, and 16 of them - or 33 per cent - responded, as defined by a set of clinical criteria.

Olaparib stopped prostate cancer growth, generating lasting falls in prostate specific antigen (PSA) levels, falls in circulating tumour cell counts in the blood, and radiological responses on CT scans and MRI.

The clinical trial found that up to 30 per cent of men with advanced prostate cancer had tumours with defects in their systems for repairing

DNA detected by genomic testing - and that these responded particularly well to olaparib.

Of the 16 patients with detectable DNA repair mutations, 14 responded very well to olaparib - accounting for the large majority of those who benefited from the drug. Most of these men, who all had terminal prostate cancer with limited treatment options, had disease control lasting much longer than expected in this group of patients.

The results have led on to the start of TOPARP-B, a second part of this trial in which only men whose prostate cancers have detectable DNA repair mutations will receive olaparib. If the results are successful, olaparib could become a standard treatment option for men with advanced prostate cancer and DNA repair mutations.

The development of olaparib, which is now owned by AstraZeneca, was underpinned by scientific research carried out with funding from Cancer Research UK at The Institute of Cancer Research (ICR) and the University of Cambridge, and clinical trials led by the ICR and The Royal Marsden, and other institutions in the UK and overseas. It has had particularly strong results in phase III trials in patients who inherited mutations to the BRCA genes, many of whom had breast or ovarian cancer.

The drug, a type of treatment called a PARP inhibitor, was licensed last year for women with ovarian cancer and inherited BRCA mutations, but so far has not been approved for use on the NHS by NICE or the Cancer Drugs Fund.

Trial chief investigator Professor Johann de Bono, Head of Drug Development at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, said:

"Our trial marks a significant step forward in the treatment of prostate cancer, showing that olaparib is highly effective at treating men with DNA repair defects in their tumours. It also proves the principle that we can detect prostate cancers with specific targetable mutations using genomic sequencing to deliver more precise cancer care by matching treatment to those men most likely to benefit.

"I hope it won't be long before we are using olaparib in the clinic to treat prostate cancer, or before genomic stratification of cancers becomes a standard in this and other cancers."

Study co-leader Dr Emma Hall, Deputy Director of the Cancer Research UK-funded Clinical Trials and Statistics Unit at The Institute of Cancer Research, London, which co-ordinated the study, said:

"This phase II clinical trial combined a highly targeted cancer drug with cutting-edge genomic sequencing. We showed that a subset of men whose tumours had mutations in their DNA repair machinery responded particularly well to treatment with olaparib. The next trial includes only men with these mutations in their tumours, with the aim of proving that olaparib is highly effective for them."

Dr Aine McCarthy, science information officer at Cancer Research UK, said:

"Even though the number of men surviving prostate cancer is increasing, it's still the second most common cause of cancer death in UK men. This is partly because the disease is so hard to treat once it has spread around the body.

"This trial is exciting because it could offer a new way to treat prostate cancer by targeting genetic mistakes in cancers that have spread. The hope is that this approach could help save many more lives in the

future."

Howard R. Soule, PhD, executive vice president and chief science officer of the Prostate Cancer Foundation, said:

"TOPARP-A is significant because it exploits the genetic similarities of prostate, breast and ovarian cancers," said. "We are excited about this pioneering study because it demonstrates the tremendous crossover and wider applications in the research on these diseases."

Dr. William Nelson, co-vice chair of the SU2C Scientific Advisory Committee and director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland, said:

"Understanding the link between prostate cancer and DNA repair mutations is incredibly important for patients and their families. We can identify prostate cancer patients who will benefit from drugs like olaparib and also help men and their families better understand their genetic risk of metastatic prostate cancer, just as women with BRCA mutations do for breast and ovarian cancer."

Provided by Institute of Cancer Research