Major trial shows breast cancer drug can hit prostate cancer Achilles heel

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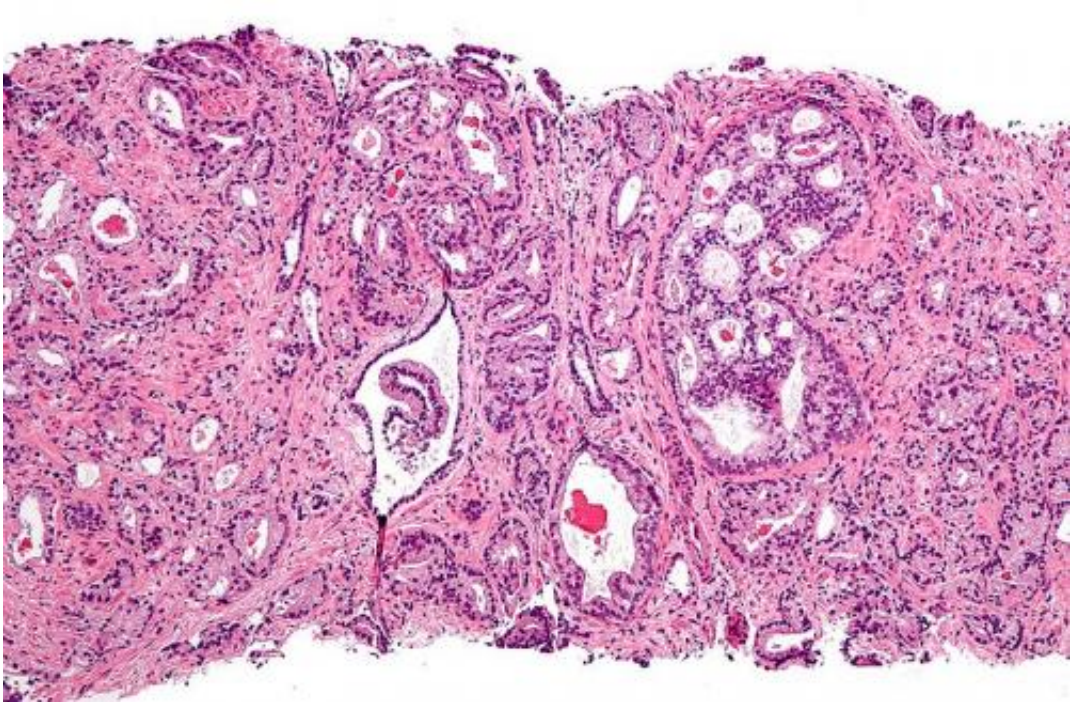

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

A drug already licensed for the treatment of breast and ovarian cancers is more effective than targeted hormone therapy at keeping cancer in check in some men with advanced prostate cancer, a major clinical trial reports.

Olaparib, a pill lacking the side effects of chemotherapy, can target an

Achilles heel in prostate cancers with a weakness in their ability to repair damaged DNA. It is now on the verge of becoming approved as the first genetically targeted treatment for prostate cancer.

This precision medicine drug, a type of treatment called a PARP inhibitor which specifically targets cancer cells with faulty DNA repair genes, blocked prostate cancer growth more effectively than the modern targeted hormone treatments abiraterone and enzalutamide.

The final results from the PROfound trial, published in the prestigious journal the *New England Journal of Medicine* today, are set to herald the landmark approval of olaparib in prostate cancer in the US and Europe this year. The study was funded by AstraZeneca.

A team from The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, alongside colleagues from all around the world including Northwestern University in Chicago, US, studied 387 men with advanced prostate cancer who had alterations in one or more of 15 DNA repair genes. The researchers found that using olaparib in this group of men with faulty DNA repair genes significantly delayed disease progression.

Men with prostate cancers that had faulty BRCA1, BRCA2 or ATM genes benefited the most from receiving olaparib—with their disease taking 7.4 months before it progressed, compared with 3.6 months for those who received enzalutamide and abiraterone.

Men with an alteration in any of the other 12 pre-selected DNA repair genes also benefitted from receiving olaparib.

Overall, for men with any of the 15 faulty DNA repair genes who were given olaparib, the length of time before their cancer got worse was 5.8 months on average, compared with 3.5 months with targeted hormonal

treatment.

The discovery of abiraterone by The Institute of Cancer Research (ICR), and its development by the ICR and The Royal Marsden, has transformed treatment for men with advanced prostate cancer.

Researchers are excited at the prospect that olaparib—which the ICR discovered how to genetically target—could be even more effective than abiraterone in selected men with DNA repair mutations.

The overall survival of men with faulty BRCA1, BRCA2 or ATM genes was 19 months on average for those who received olaparib, compared with 15 months for those who received abiraterone or enzalutamide—despite more than 80 per cent of the men who received the targeted hormone treatments switching to olaparib when their cancer progressed and spread. However, longer follow-up will be needed to show a survival improvement conclusively.

The most frequent adverse effects were anaemia and nausea, which have been associated with olaparib in the past. But overall olaparib is a well-tolerated treatment, and much kinder on patients than chemotherapy.

PROfound is the first trial to show how crucial it is to carry out genomic testing in prostate cancer patients. It is vital to identify different patient groups based on their genetics and to tailor treatment accordingly.

Researchers are now hoping to see olaparib become available on the NHS for patients with advanced prostate cancer and faulty DNA repair genes within the next two years.

Next, they will look at combining olaparib with other treatments, with the aim of improving outcomes even further.

Study co-leader Professor Johann de Bono, Professor of Experimental Cancer Medicine at The Institute of Cancer Research, London, and Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust, said:

"Our findings show that olaparib—a drug which targets an Achilles heel in cancer cells while sparing normal, healthy cells—can outperform targeted hormone treatments in some men with advanced prostate cancer.

"It's exciting to see a drug which is already extending the lives of many women with ovarian and breast cancer now showing such clear benefits in prostate cancer too. I can't wait to see this drug start reaching men who could benefit from it on the NHS—hopefully in the next couple of years.

"Next, we will be assessing how we can combine olaparib with other treatments, which could help men with prostate cancer and faulty DNA repair genes live even longer."

Peter Isard, 59, a patient at The Royal Marsden, said:

"Initially after diagnosis I went onto hormone therapy and then chemotherapy. Six months after finishing chemotherapy, my PSA rose rapidly and I was told my chance of living for two years would be quite low. I came to The Royal Marsden for a second opinion and Prof de Bono found I had a genetic mutation that would make me suitable for an olaparib trial. I've been on the drug for almost two years now. I had a number of tumours in my lymph nodes, but now there is only one that is visible and I feel incredibly lucky not to have experienced any side-effects whatsoever."

Professor Paul Workman, Chief Executive of The Institute of Cancer

Research, London, said:

"It is great to see that this treatment, which we learned how to genetically targeted at the ICR, can successfully hit an Achiles heel in some men with advanced prostate cancer. These landmark findings mean that olaparib is now set to become the first ever genetically targeted drug for the disease.

"The next step will be to find new ways to combine olaparib with other treatments in order to prevent or overcome drug resistance. It is this kind of research, which aims to target cancer's lethal ability to adapt and evolve, which we will be conducting in our pioneering Centre for Cancer Drug Discovery once it opens later this year."

More information: *New England Journal of Medicine* (2020). DOI: 10.1056/NEJMoa1911440

Provided by Institute of Cancer Research