New drug targeting DNA repair shows promise in range of advanced cancers

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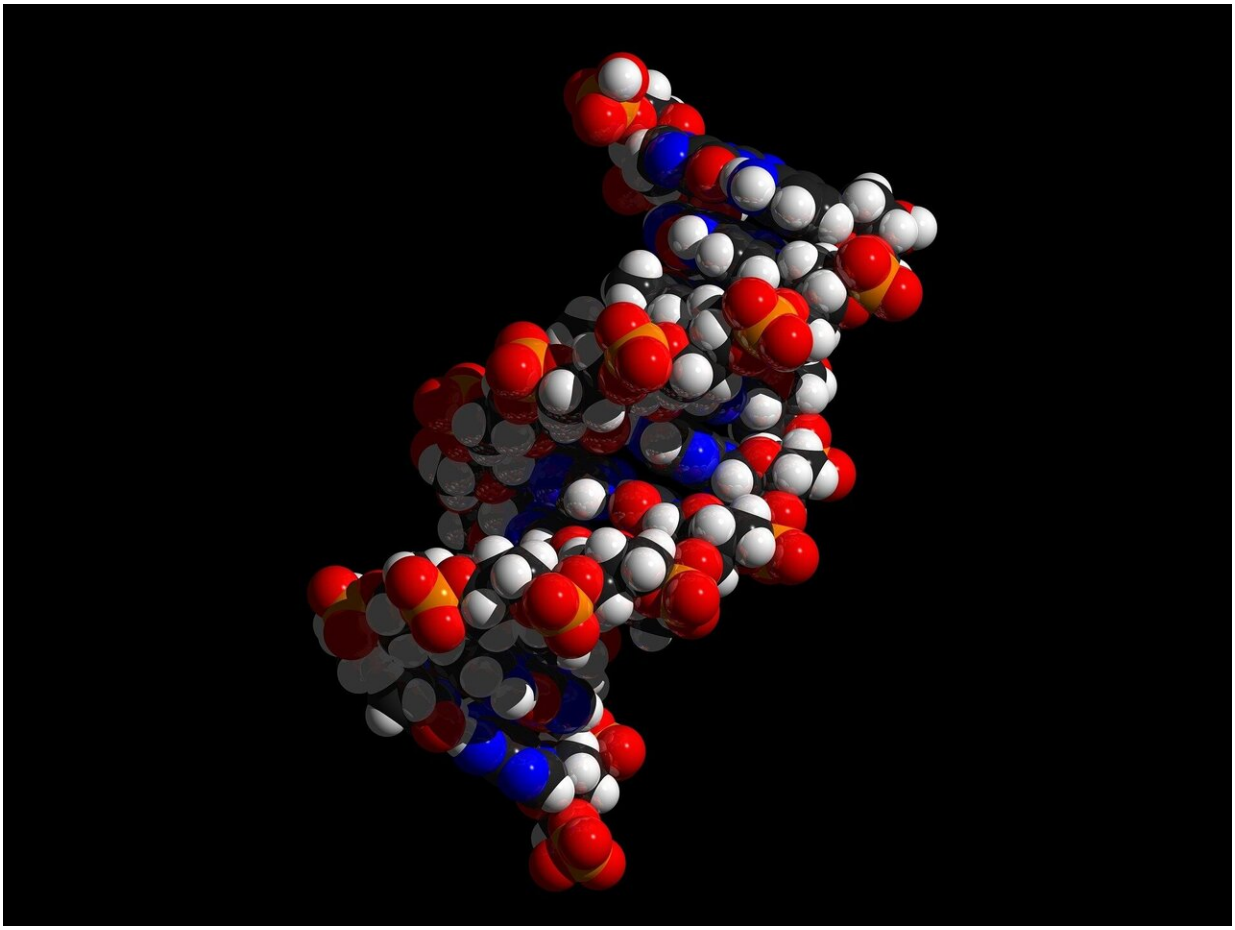

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A new precision drug which stops cancer from repairing its DNA has

shown promise in an early-stage clinical trial—highlighting the potential of a new class of drugs known as ATR inhibitors.

The drug candidate, tested in humans for the first time, was shown to be well tolerated and stopped the growth of tumors in over half of patients treated.

People in the trial had a range of advanced, heavily pre-treated cancers including breast, bowel and prostate tumors. It is remarkable to see the new drug—which works by blocking a key molecule called ATR, involved in repairing DNA—showing promising clinical benefit in a phase I trial, in patients who were very sick.

The trial, led by The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, involved 21 patients with advanced solid tumors with defects in various genes which help coordinate DNA repair. Eleven patients had tumors with defects or deletions affecting a key gene called ATM.

The aim of the trial was to evaluate the safety of the ATR inhibitor BAY1895344 and to identify the maximum tolerated dose that could be safely given to a group of cancer patients who had already previously been treated with multiple other drugs.

The researchers found that the drug was well tolerated by patients—and better still, that there were encouraging signs that it was effective against advanced cancers with defects in the ATM gene.

The new results are published in the prestigious journal *Cancer Discovery* today, and the trial was funded by the manufacturer of the drug, Bayer.

The team found that BAY1895344 stopped tumour growth in eight out

of the 21 patients and shrunk the tumors of another four patients with ATM mutations—which is remarkably positive for a phase I trial, since its primary aim is to test the safety of a drug, rather than its effectiveness.

The effectiveness of the drug seemed to be long lasting, with an average period of response of 316 days. In addition, three out of four patients who saw their tumors shrink remained on treatment for more than a year.

The most common side effect reported was anaemia, which was managed with the help of blood transfusions and did not usually require the treatment to be stopped.

The researchers also analyzed the biochemical and pharmacological effects of the drug, and were able to show that it exercised its effects in patients by increasing damage to DNA.

DNA damage is the fundamental cause of cancer—leading to mutations in key genes that allow cancer cells to divide uncontrollably. But it can also be a key weakness of tumors that can be exploited, since cancer cells can be killed by further damaging their DNA or stopping them from repairing it.

The new study supports further investigation of a treatment strategy that targets the DNA repair protein ATR, especially in patients whose cancers already have certain defects in DNA repair genes like ATM or BRCA1—weakening their ability to cope with DNA damage.

Further clinical trials are warranted to further evaluate the safety and efficacy before it can be licensed by a regulatory authority. Clinical trials investigating BAY 1895344 as a single agent or in combination with other drugs are now under way, and the hope is that it could be

developed into a new targeted treatment for patients with a variety of cancers with certain defects in DNA repair.

Recently, another phase I trial led by The Institute of Cancer Research (ICR) and The Royal Marsden also showed benefits for an ATR inhibitor (called berzosertib) in patients with very advanced tumors, either on its own or with chemotherapy.

Other cancer drugs that attack DNA repair mechanisms already exist. The ICR pioneered the genetic targeting of the first approved precision medicine attacking cancer's ability to repair DNA, the PARP inhibitor olaparib.

In future, ATR inhibitors may become a new class of targeted drugs that could help overcome resistance to other precision medicines like PARP inhibitors.

The ICR, a charity and research institute, will be focusing on how to overcome drug resistance in its new Centre for Cancer Drug Discovery, which is nearing completion. The ICR is now raising money for the Centre's state-of-the-art equipment, so that researchers in the building can get off to the strongest possible start.

Study 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 new trial shows that this promising new treatment is safe and can benefit some patients even with very advanced cancers.

"The new drug, which is currently known only by the code BAY1895344, works by blocking a molecule called ATR which is

involved in repairing DNA. It seems to be especially effective in patients whose tumors have defects in a gene called ATM which mean their ability to repair DNA is already weakened—suggesting that this could become a new form of targeted treatment.

"It is very promising to see patients responding in an early-stage trial like this, and we are looking forward to further clinical trials to test the drug's efficacy."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"It is exciting to see a new class of precision medicine showing such promise in early trials. At the ICR, we have pioneered ways of treating cancer by exploiting the weaknesses that tumors often have in repairing their DNA. I am hopeful that later-stage trials will show that this new class of ATR inhibitors can prove effective against cancers with defective systems for DNA repair, and we are keen to investigate whether they could prevent tumors from developing resistance to another important class of medicine called PARP inhibitors, which work in a similar way.

"One of our main goals is to find new targeted treatments and drug combinations that can tackle cancer evolution and drug resistance—and this will be the main focus of research in our pioneering new Centre for Cancer Drug Discovery."

More information: Timothy A. Yap et al. First-in-Human Trial of the Oral Ataxia Telangiectasia and Rad3-Related Inhibitor BAY 1895344 in Patients with Advanced Solid Tumors, *Cancer Discovery* (2020). DOI: 10.1158/2159-8290.CD-20-0868

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