New precision therapy for bile duct cancer extends patients' lives

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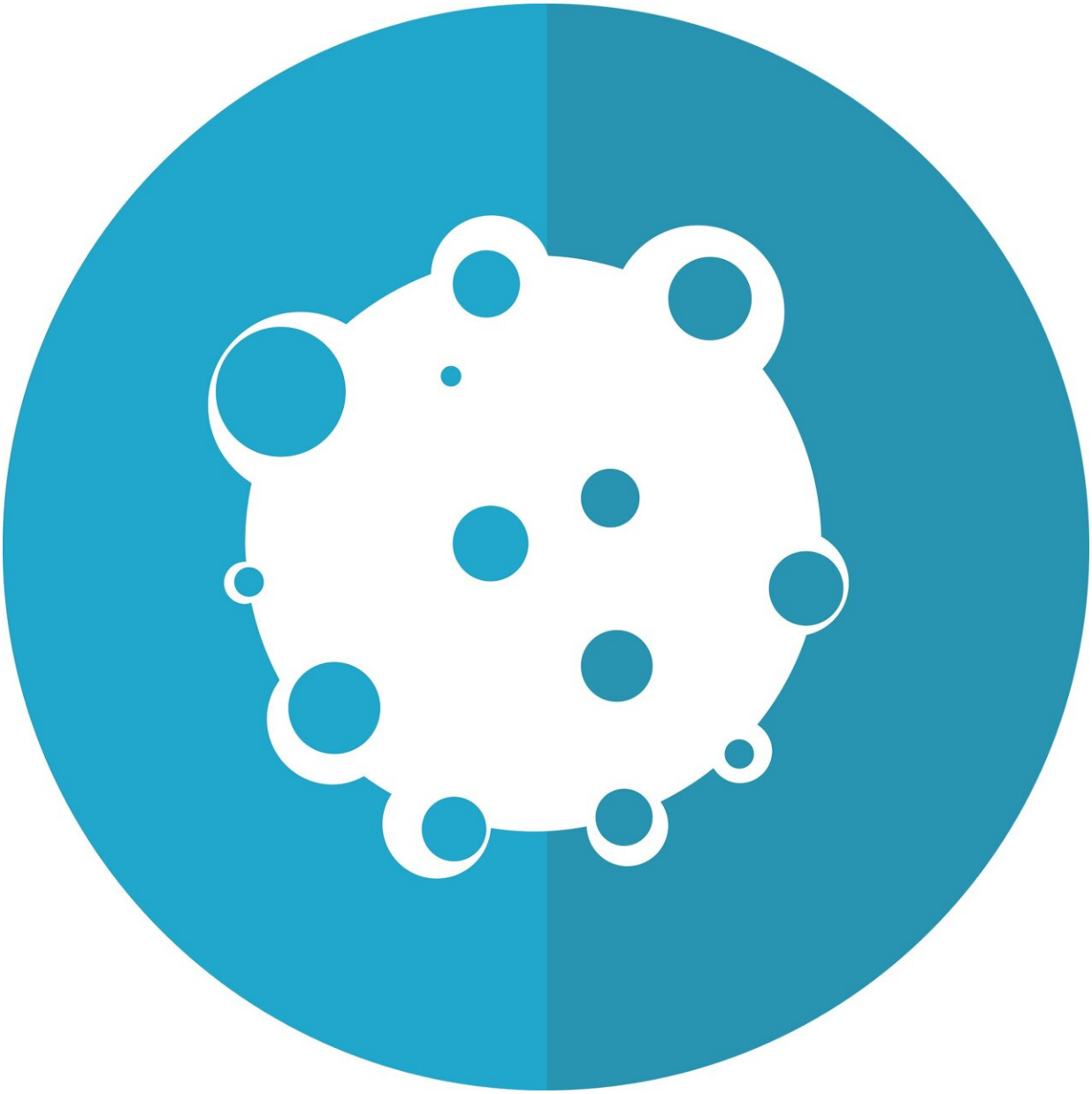

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A new personalized cancer treatment can radically improve the outlook for some patients with bile duct cancer, finds an international multicenter trial involving researchers at UCL and University College London Hospitals NHS Trust (UCLH).

The Phase II open label clinical trial—the European arm of which was led by UCL researchers—found that patients who were otherwise facing end of life care survived for up to two years when treated with the drug futibatinib.

In September last year, data from the FOENIX-CCA2 trial led to the US Food and Drug Administration (FDA) to approve futibatinib, although the UK's National Institute for Clinical Excellence has yet to consider the drug.

Set across 13 countries, the trial was sponsored by Taiho Oncology, and the results have now been published in the *New England Journal of Medicine.*

Futibatinib targets a particular genetic alteration, called FGFR2 fusion, which is found in around 14% of bile duct cancers.

Of those diagnosed annually in the UK with bile duct cancer, which comprises cholangiocarcinoma and gall bladder cancer, approximately 300 will have this genetic alteration.

There are very few treatment options for bile duct cancer and the survival is poor, with patients surviving on average for just 12 months. Although the cancer is uncommon, incidence is on the rise globally.

This international trial recruited 103 patients with bile duct cancer who had undergone at least one chemotherapy treatment, but whose cancer had become resistant. The patients' cancer tumors had been genetically analyzed (molecularly profiled) to check that they had an alteration in a particular group of genes, known as fibroblast growth factor receptors (FGFR). The drug, futibatinib, is known as an FGFR-2 inhibitor, as it targets this genetic alteration.

When the patients were treated with futibatinib (oral tablet), the results were striking. The drug was more effective at reducing the size of the tumor, with the cancer shrinking by over 40%, compared to 25% with chemotherapy. The drug also produced modest side effects compared to chemotherapy.

Patients on treatment survived for up to two years, even though they had advanced cancer and had sometimes tried up to five other treatments before entering the trial. Without this most patients would have been offered best supportive care.

European lead and senior author on the paper, Professor John Bridgewater (UCL Cancer Institute and University College London Hospitals NHS Foundation Trust) said, "These results turn treatment for this group of patients on its head. Instead of treating them with the blunderbuss that is chemotherapy, which attacks healthy cells alongside the cancer, we can offer a personalized treatment that just targets a specific alteration within the cancer.

"The benefits that patients saw in the trial were remarkable. It's important that patients with bile duct cancer get their cancer tested to find out if they have this abnormality. We can't afford to miss one of these alterations: the difference they could make to treatment outcomes is dramatic."

There are currently other FGFR inhibitors already in clinical use, including one called pemigatinib, which has been approved for use in the UK by the National Institute for Care and Health Excellence (NICE). However, existing FGFR inhibitors are known to be susceptible to resistance within the cancer. Laboratory tests have shown this is less likely to be a problem with futibatinib, as it targets the FGFR abnormality in a more specific way, and so is likely to be more effective than existing drugs.

Trials are already underway looking at the possibility of using FGFR2 inhibitors as a first line treatment in place of chemotherapy.

Professor Bridgewater said, "The question these trials now need to answer is not whether patients should be getting this treatment, but when.

"Hopefully, this kind of genetically driven treatment will become the new normal for oncology. Personalized treatment has long been a buzz word in cancer, but this trial is the real thing—proving that it can be done and bring huge benefits to specific groups of patients."

Bile duct cancer is a rare but aggressive disease in which malignant (cancer) cells form in the bile ducts; a network of tubes, which connect the liver, gallbladder, and small intestine.

Helen Morement, CEO of AMMF—The Cholangiocarcinoma Charity, explains, "The success of this trial is warmly welcomed by AMMF and the patients and clinical communities we support.

"For well over a decade there has been little in the treatment armory for those with an inoperable cholangiocarcinoma. Chemotherapy, although it can be moderately effective for some, it is not effective for all, and the effectiveness is not known until the patient has received several cycles of

chemotherapy and may have endured a number of difficult side effects, only to find there has been no advantage for them in reducing or stabilizing their cancer.

"Now for those whose cholangiocarcinoma is shown to have the FGFR2 fusion, futibatinib offers an important step forward. Not only is it a more personalized treatment which they know from the outset could have a positive impact on their cancer—bringing with it the hope of extending survival over the more standard chemotherapies and/or best supportive care that might be offered—but, as an oral therapy with tolerable side effects, it has quality of life advantages over conventional chemotherapy, including spending less time in hospital and away from loved ones.

"This important milestone emphasizes the necessity for all HCPs to put their cholangiocarcinoma patients forward for molecular testing.

"Already an approved treatment in the U.S., we now await NICE approval in due course …"

More information: Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2206834

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