Medical Xpress

Clinical trial shows tumor-starving drug improves survival of mesothelioma

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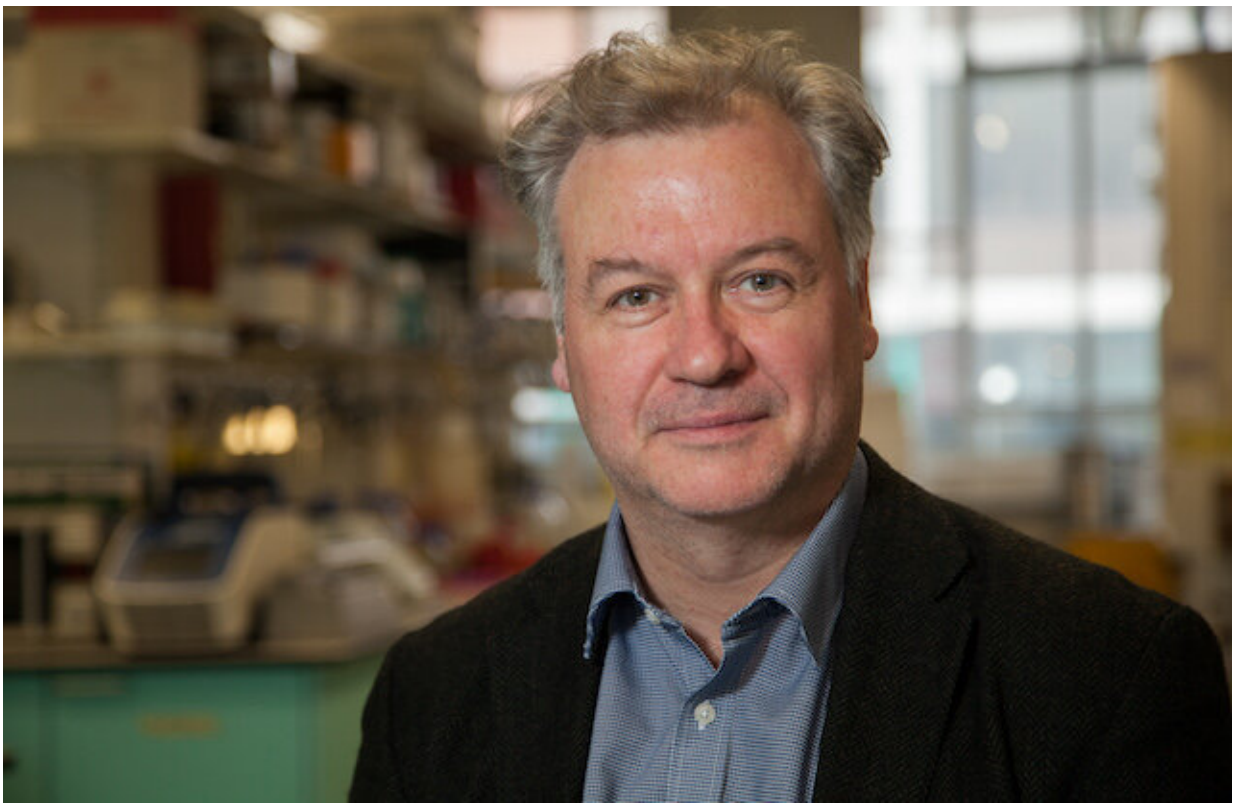

Peter Szlosarek. Credit: Queen Mary, University of London

Peter Szlosarek, Professor of Medical Oncology at Queen Mary's Barts Cancer Institute, presented his team's results from the ATOMIC-Meso clinical trial in partnership with Polaris Pharmaceuticals, Inc., at the American Association for Cancer Research Annual Meeting. The

findings show that the new drug, called ADI-PEG20, extends the median survival of patients compared with current standard treatment. This moves the drug closer to final approval by the US Food and Drug Administration (FDA), an achievement that would represent the first such approval of a new chemotherapy drug for this disease in 15 years.

The results are the culmination of 20 years of research at the Barts Cancer Institute that began with Professor Szlosarek's discovery of a key metabolic weakness in cancer cells. He and his team have since dedicated their efforts to translating this work from lab bench to patient bedside.

Malignant pleural mesothelioma (MPM) is an aggressive cancer that affects the lining of the lungs and is associated with exposure to asbestos. It has a five-year survival rate of less than 10%. MPM is usually treated with potent chemotherapy drugs, but these are seldom able to halt the progression of the disease.

Professor Szlosarek and his team launched the ATOMIC-Meso study to test a bold new approach that tackles the problem from a different angle. Cancer cells need sustenance to grow and multiply—including an amino acid called arginine that is an essential building-block for making protein. In this randomized, double-blind trial, the researchers administered a drug which depletes arginine, called pegylated arginine deiminase (ADI-PEG20). They used this treatment in combination with cisplatin and pemetrexed—the standard chemotherapy regime for pleural mesothelioma.

What did the trial show?

The ATOMIC-Meso study showed very promising results overall in patients with a type of the disease called non-epithelioid MPM. The patients who received ADI-PEG20 lived on average two months longer

than those given the placebo. What's more, one group of patients in the study have survived for more than three years, and their response to treatment will be studied further.

Although the FDA has approved new immunotherapies for mesothelioma, ipilimumab and nivolumab, in the past few years, the results of ATOMIC-Meso are expected to lead to the first new chemotherapy drug approval for treatment of mesothelioma since the licensing of pemetrexed 15 years ago.

From lab bench to bedside

Professor Szlosarek first discovered that malignant mesothelioma cells lack a protein called ASS1 two decades ago, while undertaking his Ph.D. at Barts Cancer Institute in Professor Fran Balkwill's laboratory. "I remember the moment I first saw a band on my experimental gel results that turned out to be ASS1. The rest is history," Professor Szlosarek comments.

ASS1 enables cells to manufacture their own arginine. Tumor cells lacking this molecule therefore depend on obtaining this molecule from their surroundings. ADI-PEG20 works by depleting arginine in the blood, and as a result tumor cells lacking ASS1 are starved of this essential amino acid.

Professor Szlosarek and his team first investigated the safety and efficacy of ADI-PEG20 in a clinical trial called ADAM, which reported an improvement in the median time of survival without mesothelioma progression, compared with standard chemotherapy. Subsequent laboratory research by Professor Szlosarek and his team and a phase 1 trial named TRAP revealed that a combination of cisplatin, pemetrexed and ADI-PEG20 doubled the tumor shrinkage rate in patients with aggressive mesotheliomas with excellent safety. Following this success,

TRAP progressed to the current phase 2/3 ATOMIC-meso trial.

"I don't think we could have achieved this anywhere else," Professor Szlosarek comments. "My initial exploratory lab work depended on the expertise and collaborative environment we have here at the Barts Cancer Institute. And our close ties with our hospital partners at Barts Health NHS Trust gave us access to the populations of patients with mesothelioma that were crucial to running these clinical trials."

Looking to the future

While ADI-PEG20 is effective in treating MPM, some cancer cells develop resistance to the drug after six months or more of treatment. Further research conducted at the Barts Cancer Institute in collaboration with Dr. Sarah Martin's group has shown that combining ADI-PEG20 with a molecule called spermidine-analog GC7 gives positive results in treating these resistant cells.

Professor Szlosarek's exciting results also herald new possibilities to treat other forms of MPM. Following on the heels of ATOMIC-Meso, further studies are planned of ADI-PEG20 in patients with epithelioid MPM and small cell lung cancer, another aggressive lung cancer that is dependent on arginine. Ultimately, the hope is that this new therapy could also be tested in many different forms of cancer, opening the possibility of bringing improvements in survival to many more people with the disease.

Provided by Queen Mary, University of London