Drug combination shows promise against cancer's 'death star' protein

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A drug combination targeting multiple mutant versions of cancer's "death star" protein has shown promise in a small, early-phase clinical trial for some patients with advanced lung, ovarian and thyroid cancer.

The two-drug combination was effective against advanced cancers with a range of mutations to the KRAS gene—dubbed the "death star" because its protein drives one in four cancers and has a largely impenetrable, drug-resistant surface.

The phase I trial tested the drugs VS-6766 and everolimus in 30 patients with a range of mutations to KRAS—including 11 with highly advanced, non-small cell lung cancer.

Half of the group of patients with lung cancer have not yet seen their cancer progress at six months—about twice as long as the expected benefit of chemotherapy at such an advanced stage of disease.

The research was led by a team from The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust and is being presented today (Monday) at the American Society of Clinical Oncology (ASCO) 2022 annual meeting.

Innovative dosing schedule

Previous trials which aimed to drug multiple KRAS variants in a similar way did not succeed because of severe side effects in patients. The current trial uses an innovative dosing schedule to limit toxicity. Patients received the two drugs twice weekly for three weeks, followed by a week off.

Patients on the trial had already received several prior cancer treatments including chemotherapy and state-of-the-art immunotherapy. But their cancers stopped responding because they had adapted to treatment and evolved drug resistance.

Yet the new drug combination shrank tumors by more than 30% in two of the 11 patients with lung cancer, and controlled tumor growth in nine.

It also produced responses in patients with advanced ovarian and thyroid cancers—and the researchers plan to further expand this cohort.

Some 40% of lung cancers, 45% of bowel cancers and 90% of pancreatic cancers are driven by mutant versions of KRAS.

Until recently KRAS mutations were extremely difficult to target. The first effective drug was approved in the U.S. in 2021, but it can only target one variant of KRAS called G12C. Of patients with KRAS driven lung cancer, only 40 percent have a G12C mutation, meaning the majority cannot benefit from currently available KRAS targeted drugs.

Opening up treatment options

Rather than drugging KRAS itself, VS-6766 and everolimus render KRAS less effective by simultaneously blocking the two pathways that KRAS relies upon to drive growth. This means the drug combination may also target cancers that are driven by many other KRAS mutations, opening up treatment options for other patients for whom current treatments have stopped working.

Targeting KRAS-fueled cancer in two separate ways aimed to delay the evolution of drug resistance and prevent cancer from progressing. Identifying unique treatment combinations that can counter cancer's ability to develop treatment resistance is a major focus of scientists at The Institute of Cancer Research (ICR).

More information: Phase I trial of the RAF/MEK clamp VS-6766 in combination with everolimus using an intermittent schedule with expansion in NSCLC across multiple KRAS variants. meetings.asco.org/abstracts-presentations/209970

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