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Three drugs may be better than one for certain patients with advanced colorectal cancer

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Patients with a form of advanced colorectal cancer that is driven by a mutated version of the BRAF gene have limited treatment options available. However, results from a multi-centre clinical trial suggest that the cancer may respond to a combination of three targeted drugs.

Professor Josep Tabernero, head of the medical oncology department at Vall d'Hebron University Hospital and director of the Vall d'Hebron Institute of Oncology, Barcelona, Spain, will tell the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona today (Friday) that he and colleagues in a number of different countries are investigating a BRAF inhibitor, encorafenib, combined with cetuximab, which inhibits the epidermal growth factor receptor (EGFR), with or without a third drug, alpelisib, which inhibits another cancer-causing pathway called PI3K, in a phase I clinical trial for patients with advanced BRAF-mutated colorectal cancer.

"Among the 54 patients enrolled in the dose-finding part of the trial, we found that tumours shrank in 23% of the patients receiving encorafenib and cetuximab, and in 32% of patients receiving a combination of all three drugs," he will say. "The median length of time that patients survived without their disease worsening ranged from 16 weeks for patients receiving the dual therapy to 19 weeks for those receiving all three drugs. While we were not comparing patients on these therapies with patients receiving the normal standard of care, these progression-

free survival times are nearly double those for patients who have been treated in the past with standard of care therapies."

He will continue: "Patients with advanced colorectal cancer with tumours that bear BRAF mutations invariably fail to respond meaningfully to standard treatments and ultimately face a dismal prognosis. Further, recent efforts aimed at using a single agent to inhibit BRAF in colorectal tumours have largely disappointed in improving response to therapy in these patients. Spurred by promising preclinical results, and in order to avoid mechanisms of primary resistance to therapy, we have tested the safety and efficacy of a novel approach to treatment, combining a 'trio' of existing therapies in patients.

"While it is still early days and these are preliminary data, this combinatorial strategy is showing improved efficacy, extended progression free survival, with manageable side-effects in patients. This study, therefore, represents a significant step forward in providing metastatic colorectal cancer patients with fresh hope and a new therapeutic avenue."

Patients on the trial were treated with encorafenib, taken orally once a day, together with a standard intravenous dose of cetuximab (400 mg/m2 for the initial, loading dose, followed by 250 mg/m2 weekly). In addition, 28 of the patients also received an oral dose of alpelisib once a day.

The researchers found that the combination of drugs was generally well tolerated by the patients. Adverse side-effects for the dual therapy included fatigue, reactions to the infusion and low phosphate levels in the blood. The addition of alpelisib also caused nausea, diarrhoea, skin rashes, high blood sugar levels and increased levels of lipase (a protein released by the pancreas that helps the body to absorb fat).

The genetic make-up of the tumours was analysed to see how this compared with the responses to treatment seen in the patients. "This work has shown that BRAF-mutated colorectal cancer is a diverse disease and that a number of key, cancer-related pathways are involved, including the PI3K and WNT pathways," says Prof Tabernero. "This could explain why drugs that target different pathways are more effective when used together."

The trial is continuing to enrol patients - up to 50 for each arm of the trial - randomising them to either the dual or triple combination of drugs in order to see which is the most promising regimen.

Professor Jean-Charles Soria, chair of the scientific committee for the EORTC-NCI-AACR Symposium and Director of the Site de Recherche Intégrée sur le Cancer (SIRIC) Socrate project at Gustave Roussy Cancer Campus, France, commented: "BRAF mutants represent a genetically well-defined sub-group of colorectal cancers. In such patients monotherapy with BRAF inhibitors lacks activity in clear contrast with the indisputable activity observed in BRAF mutant melanoma or non-small cell lung cancer. Here a dual blockade of BRAF and EGFR, as well as a triple blockade of BRAF, EGFR and PI3K demonstrate clear anti-tumour activity in the vast majority of patients with tumour shrinkage in 25-30% and stable disease in 54-60%."

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