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Anti-PD-L1 immunotherapy responsive in microsatellite-stable mCRC comb with MEK inhibition

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Anti-PD-L1 immunotherapy may achieve a response in patients with microsatellite-stable metastatic colorectal cancer if combined with a MEK inhibitor, according to phase I data presented at the ESMO 18th World Congress of Gastrointestinal Cancer in Barcelona, Spain.

"So far, immunotherapy has only shown activity in patients with microsatellite instability-high colorectal cancer, which is only 5% of the population," says the study's principal investigator Dr Johanna Bendell, from the Sarah Cannon Research Institute and Tennessee Oncology, in Nashville, Tennessee.

Microsatellite instability-high colorectal cancers are associated with a greater number of mutations and are therefore more responsive to immunotherapy with PD-L1/PD-1 blockade. However the majority of patients with metastatic colorectal cancer - around 95% - have microsatellite-stable disease that so far has shown almost no response to immunotherapy.

Preclinical studies have suggested that a MEK inhibitor can make a tumor more responsive to immunotherapy by increasing the number of active immune cells - such as CD8+ cells - in the tumor, and increasing the expression of factors that cause the immune system to be more active.

In this phase 1b study, 23 previously-treated patients with metastatic colorectal cancer were treated with escalating doses of MEK inhibitor cobimetinib (20mg, 40mg, and 60mg daily, 21 days on, 7 days off), with an expansion of patients at the highest dose level, and a 800mg dose of intravenous PD-L1 inhibitor atezolizumab every two weeks.

Following treatment, researchers saw a decrease of at least 30% in tumor size in four patients (17%) and stable disease in five patients (22%). The duration of responses ranged from 4 months to over 15 months, and were still ongoing in two of four patients who were partial responders at the time of the data cut.

Three of the partial responders had microsatellite-stable or microsatellite instability-low disease and one had unknown microsatellite status. None of the patients in the study had known microsatellite high disease.

The baseline PD-L1 status did not appear to affect responses, and the combination was well tolerated with no serious treatment-related adverse events reported.

In summary, Dr Bendell says, "What we saw is consistent with the hypothesized mechanism of action of this combination, which shows promise in giving the other 95% of colon cancer patients a chance to respond to immunotherapy." Researchers have now launched a randomized phase III study to compare the combination with standard treatment for patients with refractory metastatic colorectal cancer.

Commenting on the findings, Professor Florian Lordick, Director of the University Cancer Centre Leipzig, Germany, says "this important phase 1b study now shows for the first time that metastatic colorectal cancer can be sensitized for immune therapy by inhibition of MEK-dependent intracellular signaling."

"This is the first step for immunotherapy to reach patient populations who previously were not identified as good candidates for immune checkpoint inhibition," Professor Lordick says.

More information: Abstract LBA-01 - 'Safety and efficacy of cobimetinib (cobi) and atezolizumab (atezo) in a Phase 1b study of metastatic colorectal cancer (mCRC)' will be presented by Johanna Bendell during Session I: Opening, Selected Abstracts, and Lectures on Nutrition on Wednesday 29 June, 14:50 (CEST).

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