Patients with metastatic colorectal cancer may continue benefiting from immunotherapy after treatment discontinuation

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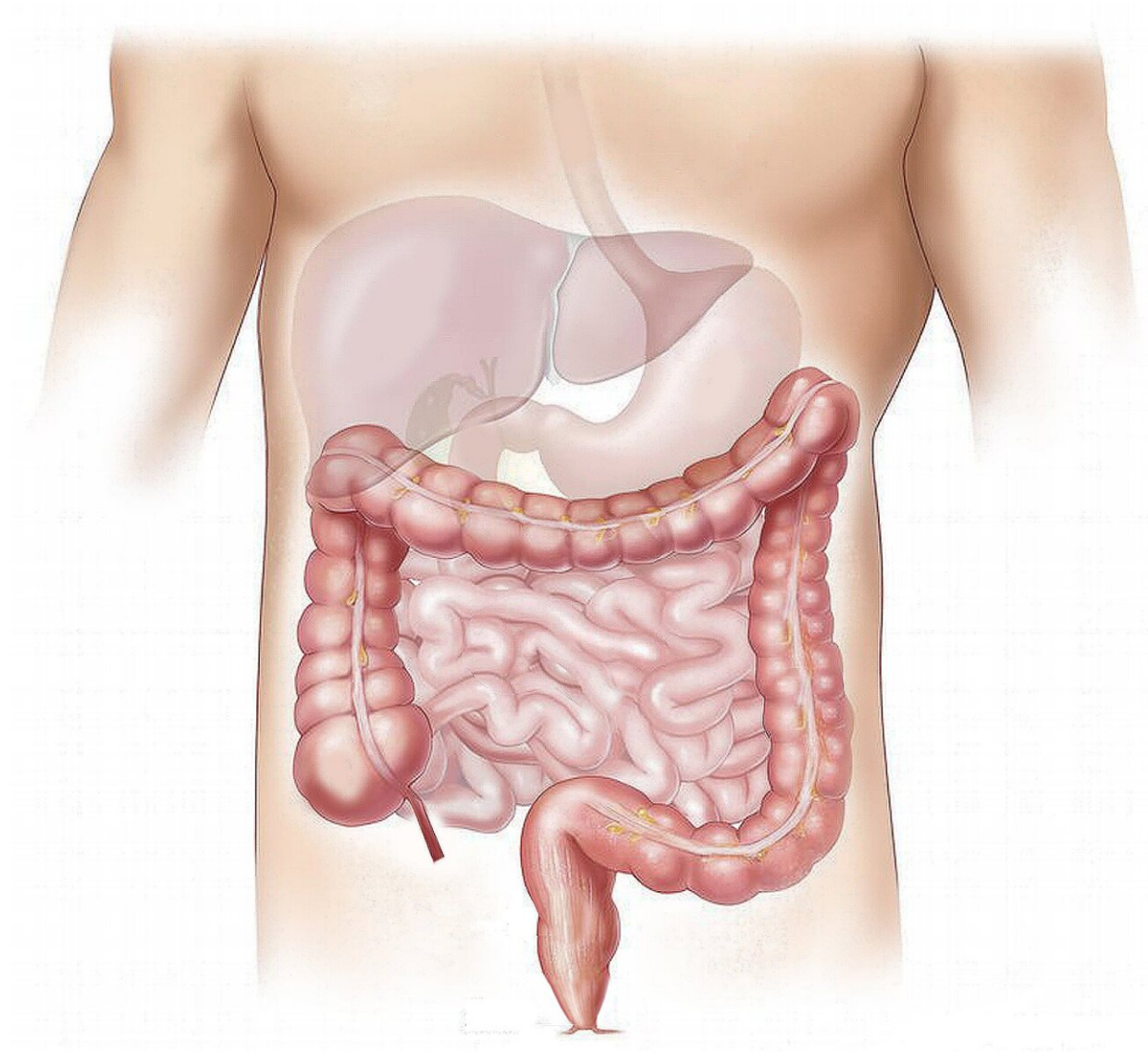

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The majority of patients with metastatic colorectal cancer whose cancer did not progress during initial treatment with immune checkpoint inhibitors (ICIs) had no disease progression two years after discontinuing treatment, reports a new study.

The study is published in the journal *Cancer Research Communications*.

ICIs have proven effective against certain solid tumors, including those with a high microsatellite instability (MSI-H) or deficient DNA mismatch repair (dMMR) status. To date, four ICIs have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced MSI-H/dMMR colorectal cancer.

When patients' colorectal tumors shrink or remain stable during ICI treatment, physicians may discontinue their immunotherapy after two years. Some patients may also cease ICI therapy earlier due to unmanageable side effects. Stopping a treatment regimen that was working can make patients nervous that the benefits will stop as well, Morris explained.

"Patients very understandably get afraid at the prospect of stopping a therapy which appears to be working and often does not cause many side effects. They've had a diagnosis of stage 4 colorectal cancer, and they wonder about the chance of their cancer coming back if they stop treatment," Morris said. "When we set out to do this study, we didn't know the odds."

Morris and colleagues performed a retrospective analysis of 64 patients with MSI-H/dMMR metastatic colorectal cancer who were treated with an ICI targeting PD-1 or PD-L1, alone (48 patients) or in combination with an ICI targeting CTLA-4 (16 patients). All patients had experienced a durable benefit at the time of treatment cessation; 48 patients discontinued treatment due to a prolonged benefit, and 16 discontinued treatment due to side effects. Patients had received ICI therapy for a median of 17.6 months.

At a median of 22.6 months after stopping immunotherapy, 88% of patients had not experienced a recurrence. The progression-free survival rate after cessation of immunotherapy was 98% at one year, 91% at two years, and 84% at three years post-treatment. The rates were not significantly different whether patients had discontinued treatment due to side effects or due to a prolonged response.

The researchers investigated other factors that could influence the likelihood of relapse after treatment cessation. No significant differences in progression rates were observed whether patients had received single-agent or combination ICI therapy; whether or not they had metastases to the liver, peritoneum, or lymph nodes; and whether or not their tumors had mutations in KRAS, NRAS, or BRAF. Patients with lung metastases had a higher chance of recurrence than patients without lung metastases, a finding Morris said requires further investigation.

Seven of the eight patients whose tumors progressed after stopping treatment were placed back on ICI therapy. Of note, all seven patients experienced a response or stable disease following rechallenge with ICIs.

Morris suggested that these data may alleviate the fears of physicians who may not want to discontinue a patient's treatment because of high-risk tumor characteristics. "We often hear from oncologists that they

don't feel comfortable stopping treatment on a patient with a BRAF mutation, for instance. But we did not see any association between mutation status and the likelihood for the cancer to recur," Morris said.

"These data provide important information that oncologists can use for guiding discussions with patients with MSI-H/dMMR colorectal cancer by providing clearer numbers for the likelihood of progression should they decide to stop their immunotherapy treatment," he continued. "If you tell patients that, based on these data, there's an 88% chance that their cancer won't come back if they come off of therapy, I think they may be more accepting of that decision to stop treatment."

Limitations of this study include its retrospective nature, as well as the relatively small sample size, which limits the statistical power of subgroup analyses. Further, the cohort included patients from a single cancer center, which may limit the applicability of the data to patients in other locations.

More information: Kristen Simmons et al, Sustained Disease Control in Immune Checkpoint Blockade Responders with Microsatellite Instability-high Colorectal Cancer after Treatment Termination, *Cancer Research Communications* (2023). DOI: 10.1158/2767-9764.CRC-23-0340