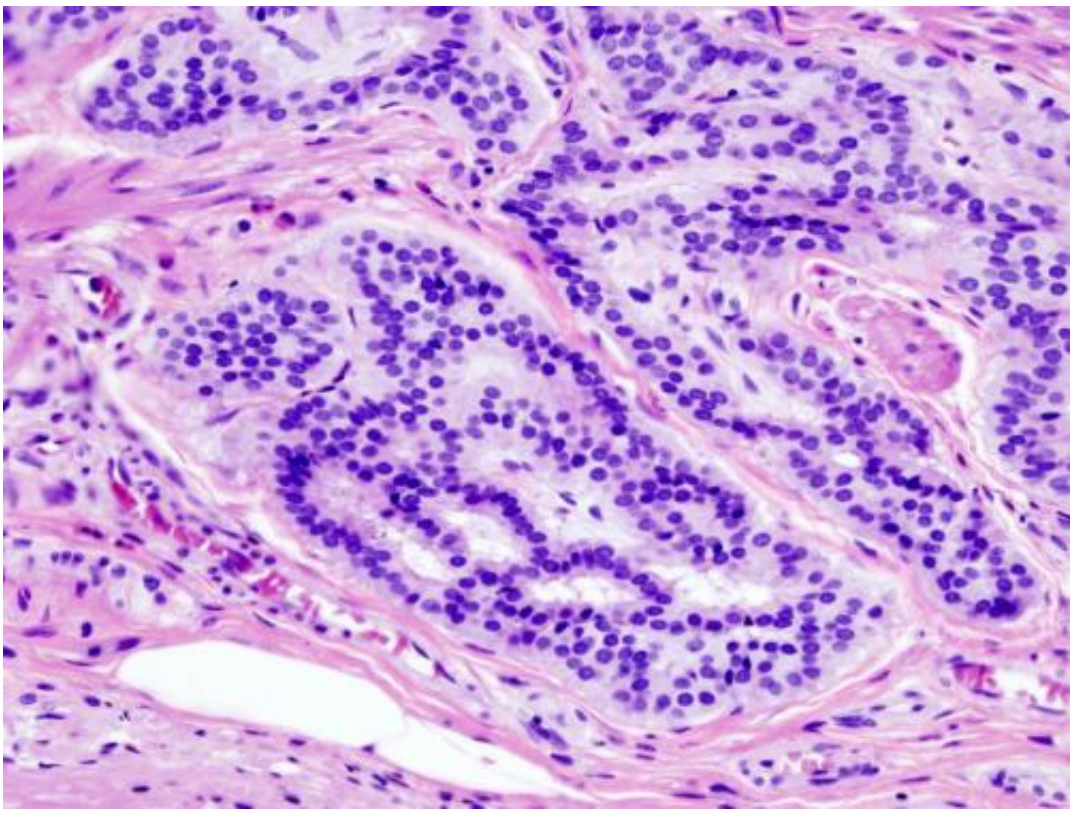
Immunotherapy may become new first line treatment in some metastatic colorectal cancers

October 22 2018



Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

Immunotherapy with nivolumab and low-dose ipilimumab could become a new first line treatment in patients with some metastatic colorectal

cancers following late-breaking results from the CheckMate-142 trial reported at the ESMO 2018 Congress in Munich. The drug combination shrank tumours and had beneficial effects on survival in patients with microsatellite instabiliy (MSI)-high metastatic colorectal cancer.

Around 4 percent of metastatic colorectal cancers are MSI-high, also called mismatch repair deficient. This means that tumour cells have mutations in the genes that usually repair DNA. Patients with MSI-high tumours have shorter survival (~14–19 months) than those with non-MSI-high tumours (~17–25 months), when treated with chemotherapy in a first-line setting.

The phase II CheckMate-142 trial previously showed that in patients with MSI-high metastatic colorectal cancer that is resistant to chemotherapy, immunotherapy with nivolumab and low-dose ipilimumab provided durable clinical benefit and manageable side effects, leading to approval by the US Food and Drug Administration (FDA).

Today researchers report for the first time the CheckMate-142 results in patients who have received no prior treatment for MSI-high metastatic colorectal cancer. The study enrolled 45 patients. The median age was 66 years and 51 percent were male. Patients were followed-up for a median of 13.8 months for the primary endpoint of objective response rate.

The objective response rate was 60 percent and 7 percent of patients had a complete response. Some 84 percent of patients had tumour shrinkage. It took a median of 2.6 months to respond to treatment. The median duration of response, median progression-free survival, and median overall survival have not yet been reached. The 12-month progression-free survival and overall survival rates were 77 percent and 83 percent, respectively.

Other trials have tested high-dose ipilimumab combined with nivolumab, but CheckMate-142 used low-dose ipilimumab with nivolumab, which resulted in less toxicity. Treatment-related grade 3 and 4 toxicities were reported in 16 percent of patients and 7 percent discontinued therapy due to treatment-related adverse events.

Study author Prof Heinz-Josef Lenz, Co-Leader, Gastrointestinal Cancers Program, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, US, said: "The combination of low-dose ipilimumab and nivolumab has a durable clinical response and is well tolerated as first line treatment in patients with MSI-high metastatic colorectal cancer. The data suggest that nivolumab and ipilimumab may be a first line treatment option for these patients."

Commenting on the results for ESMO, Prof Thierry André, Head of Medical Oncology, Hôpital Saint-Antoine, Assistance Publique – Hôpitaux de Paris, France, said: "Nivolumab plus low-dose ipilimumab is effective in most patients with MSI-high metastatic colorectal cancer. Patients improve dramatically and some return to work. It means healthcare systems can be confident that resources are being targeted effectively. This is in contrast to other metastatic cancers (melanoma, lung or kidney) where it is more difficult to select patients who benefit from immunotherapy."

André noted that these phase II results could lead the manufacturer to ask the FDA to approve this immunotherapy combination for the first line treatment of MSI-high metastatic colorectal cancer, but the European Medicines Agency (EMA) will probably require a randomised phase III trial. The ongoing phase III KEYNOTE-177 study in MSI-high metastatic colorectal cancer is comparing first line treatment with pembrolizumab versus chemotherapy with or without targeted therapy and the first results are expected in 2019. André said: "Another question

is whether the combination of nivolumab and ipilimumab is superior to nivolumab alone for the first line treatment of patients with MSI-high metastatic colorectal cancer. Previous results from CheckMate-142 suggest, with indirect comparisons, improved efficacy with nivolumab plus low-dose ipilimumab relative to nivolumab alone in previously treated patients with MSI-high metastatic colorectal cancer."

More information: Volker Heinemann et al. Somatic DNA mutations, tumor mutational burden (TMB), and MSI Status: Association with efficacy in patients (pts) with metastatic colorectal cancer (mCRC) of FIRE-3 (AIO KRK-0306)., *Journal of Clinical Oncology* (2018). DOI: 10.1200/JCO.2018.36.15_suppl.3591

S. Venderbosch et al. Mismatch Repair Status and BRAF Mutation Status in Metastatic Colorectal Cancer Patients: A Pooled Analysis of the CAIRO, CAIRO2, COIN, and FOCUS Studies, *Clinical Cancer Research* (2014). DOI: 10.1158/1078-0432.CCR-14-0332

Michael J. Overman et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer, *Journal of Clinical Oncology* (2018). DOI: 10.1200/JCO.2017.76.9901

Provided by European Society for Medical Oncology

provided for information purposes only.