# Opdivo Plus Yervoy Works Well Against Colon Cancer With Genetic Mutations

Immunotherapy combo provided durable benefit for people with advanced colorectal cancer.

January 25, 2018 By Liz Highleyman

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Combining Opdivo (nivolumab) and Yervoy (ipilimumab)—two drugs that target different immune checkpoints—led to tumor shrinkage in more than half of treated patients with mismatch repair deficient or microsatellite instability-high colorectal cancer, according to research presented at the 2018 Gastrointestinal Cancers Symposium (GI18) last week in San Francisco.

The overall survival rate at one year was 85 percent, and most responders were still on treatment and doing well when the study data were analyzed, Thierry André, MD, of Saint-Antoine Hospital in Paris reported.

Colorectal cancer is the third leading cause of cancer-related death for both men and women in the United States, and death rates appear to be increasing among people under 50. Although regular screening for colon cancer is recommended, it is often caught at a late stage and can be difficult to treat.

Bristol-Myers Squibb's CheckMate-142 trial evaluated Opdivo, alone and with Yervoy, in previously treated people with colorectal cancer that had metastasized (spread beyond the colon and rectum) or relapsed after chemotherapy.

Genetic testing showed that study participants' tumors had deficiencies in their DNA mismatch repair (dMMR) system, leading to so-called microsatellite instability, or predisposition to mutations. Tumors with a broken mismatch repair system are unable to fix genetic damage that halts cancer cell multiplication.

Mismatch repair deficiency mutations and high microsatellite instability (dMMR/MSI-H for short) occur in several types of tumors, including about 4 percent of metastatic colon cancers, according to André. Last year, the Food and Drug Administration approved Keytruda (pembrolizumab), a medication in the same class as Opdivo, for all cancers with this mutation—the first time a treatment has been approved to treat cancer regardless of where it occurs in the body.

Opdivo is a monoclonal antibody that blocks the PD-1 receptor, an immune checkpoint on T cells that plays a role in regulating immune function. Some tumors can hijack PD-1 to turn off immune

responses against them, and drugs like Opdivo release the brakes and restore T-cell activity. Yervoy blocks a different immune checkpoint, CTLA-4, which turns off immune responses by suppressing T-cell multiplication.

As reported last year, the first part of the CheckMate-142 trial showed that Opdivo alone produced clinically meaningful responses and disease control in previously treated patients with dMMR/MSI-H metastatic colorectal cancer.

The Opdivo monotherapy group included 74 patients. About 60 percent were men, the median age was 53 and 45 percent had Stage IV (the most advanced disease stage) at diagnosis. They had all used at least one prior therapy and half had tried three or more. They received Opdivo at a dose of 3 milligrams per kilogram every two weeks until disease progression or unacceptable toxicity.

At GI18, Michael Overman, MD, of the University of Texas MD Anderson Cancer presented follow-up data showing that Opdivo continued to provide durable responses and long-term overall survival. (These results were simultaneously published in the Journal of Clinical Oncology.)

After a median 21 months of follow-up, the overall response rate—meaning complete or partial tumor shrinkage—was 34 percent. This included seven people (9 percent) with complete responses, up from two patients (3 percent) at the 13-month analysis. In addition, 32 percent had stable disease.

André presented findings from another CheckMate-142 cohort that received Opdivo plus Yervoy, based on research showing that the two drugs appear to have synergistic activity—meaning they make each other more effective—in people with melanoma and lung cancer.

The combination therapy cohort included 119 people. About 60 percent were men, the median age was 58 and they had used at least one prior therapy. They received the same dose of Opdivo plus 1 mg/kg Yervoy every three weeks for four doses, followed by Opdivo alone every two weeks. The median follow-up period was about 13 months and two thirds were still on treatment. Nineteen percent stopped treatment because of disease progression and 13 percent did so due to side effects.

The overall response rate was 55 percent, including 3 percent with complete responses. Another 31 percent had stable disease. The combined disease control rate among those treated for at least 12 weeks was 80 percent. Response rates were similar regardless of tumor PD-L1 expression (the binding partner of PD-1) or other mutations including BRAF and KRAS. The median duration of response in the combination cohort could not be determined, as 94 percent of responders had ongoing responses when the data were analyzed.

The overall response, complete response and disease control rates were higher in the combination therapy cohort than those seen in the group treated with Opdivo alone, although the study was not designed to formally compare these two groups, according to André.

After one year of treatment, the progression-free survival rate—meaning patients were still alive

without worsening of disease—was 71 percent, and the overall survival rate was 85 percent. The median overall survival could not yet be determined because most patients are still living.

André also noted that study participants reported meaningful improvements in quality of life using standard measurement scales.

Side effects were common, but a majority were mild or moderate. About a third of participants taking the combination regimen reported severe treatment-related adverse events. The most common side effects were diarrhea, fatigue, itching and fever. Severe side effects (32 percent versus 20 percent) and side effects leading to treatment discontinuation (13 percent versus 7 percent) occurred more often in the combination cohort than in the group receiving Opdivo alone.

Opdivo plus Yervoy "represents a promising new treatment option for patients with previously treated dMMR/MSI-H metastatic colorectal cancer," the researchers concluded.

"The combination of Opdivo and Yervoy may represent an important advance for these distinct biomarker-defined patients, who historically have poorer outcomes compared to metastatic colorectal cancer patients whose tumors are mismatch repair proficient or microsatellite stable," André said in a Bristol-Myers Squibb press release.

Click here to read the GI18 Opdivo plus Yervoy abstract.

Click here to read the Bristol-Myers Squibb press release about the study.

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