

A Report From the American Society of Clinical Oncology 2007 Annual Meeting

Colorectal Cancer

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Each year, approximately 154,000 Americans will be diagnosed with colorectal cancer. In the United States it is the fourth most common cancer in men and women. Caught early, doctors can treat it effectively. Colorectal cancer is more common in people over 50, and the risk increases with age. Other risk factors include:

- Polyps—growths inside the colon and rectum that may become cancerous
- A diet high in fat
- A history of colorectal cancer
- A history of ulcerative colitis or Crohn’s disease

The most visible symptom of colorectal cancer—blood in the stool—may not appear during the early stages. And some people may experience common symptoms that they might not associate with colorectal cancer such as a change in bowel habits, cramping or steady stomach pain, or weakness and tiredness. For these reasons it’s important that everyone who is 50 or older be screened.

Advanced Colorectal Cancer

ADDING CETUXIMAB (ERBITUX) TO TREATMENT FOR ADVANCED COLORECTAL CANCER

Over the past 10 years, people who have received treatment for colorectal cancer are living longer than ever before. As a result, quality of life has become more important to these patients and the doctors who treat them. According to two large clinical trials, the drug cetuximab (Erbix) is an effective option for improving the quality of life of people with advanced colorectal cancer.

Early results are in for the first study known as EPIC, an international clinical trial with North American and European researchers. EPIC has shown that adding cetuximab to treatment that contained irinotecan (Camptosar) shrank tumors in people with advanced colorectal cancer. These medications

What’s New, What’s Important

- Adding cetuximab (Erbix) to treatment for people with advanced colorectal cancer not only slows or stops the growth of their tumors, it also seems to improve their quality of life by reducing pain, nausea, and difficulty sleeping.
- Adding cetuximab to FOLFIRI chemotherapy is a promising first-line treatment option for people with advanced colorectal cancer. It has not yet been approved by the U.S. Food and Drug Administration for use in this type and stage of cancer.
- People with advanced colorectal cancer who received FOLFOX treatment lived longer than those who received standard treatment. In conjunction with surgery, FOLFOX treatment appears to be so effective in lowering the risk of the cancer returning to the liver in people with metastatic colorectal cancer that it may become the standard of care.

increased the amount of time before their cancer grew. The researchers also found that this combination treatment helped reduce pain, nausea, and difficulty sleeping.

Nearly 1,300 people took part in the EPIC clinical trial. These patients had **metastatic** colorectal cancer that did not respond to first treatment with oxaliplatin (Eloxatin)-based chemotherapy. About 650 people received cetuximab plus irinotecan, and 650 patients received irinotecan alone. The growth of tumors was slowed or stopped in approximately 60 percent of those treated with cetuximab, compared with only about 45 percent of those not treated with cetuximab.

Another clinical trial, conducted by the National Cancer Institute of Canada and the Australasian Gastro-Intestinal Trials Group, also showed quality-of-life benefits of cetuximab. More than 575 people with metastatic colorectal cancer received cetuximab plus supportive care (also called comfort care, designed to improve the quality of life by treating side effects), or just supportive care alone. After eight and 16 weeks of treatment,

those who were given cetuximab experienced improvement in their physical function and overall level of health.

CHEMOTHERAPY AND CETUXIMAB FOR ADVANCED COLORECTAL CANCER

Although cetuximab has been approved as a treatment for colorectal cancer that has spread to other parts of the body, researchers wanted to know how effective it would be for people whose advanced colorectal cancer had never been treated before. (Doctors call this **first-line** treatment.) In the CRYSTAL trial, European researchers conducted a study that included almost 2,000 people with advanced colorectal cancer. Not only had these patients never been treated, they could not have surgery for their cancer.

The clinical trial participants were divided into two groups. The first group of more than 1,000 patients received cetuximab along with a standard three-drug chemotherapy combination known as **FOLFIRI** (irinotecan, leucovorin [Wellcovorin], and 5-fluorouracil [5-FU]). The second group of about 600 patients received just FOLFIRI.

Adding cetuximab produced several positive results. First, the combination treatment reduced (by about 15 percent) the risk of the cancer growing. Second, tumors shrank by half or more in about 47 percent of the cetuximab group, compared with only about 39 percent of those not treated with cetuximab. Third, more patients treated with cetuximab were able to have surgery to treat their cancer (nearly 4½ percent) compared with the number of patients who were treated with only FOLFIRI (1½ percent). In other words, with cetuximab treatment, the tumors shrank enough to make surgery an option.



Researchers are very encouraged by these findings. In the future, this combination treatment might be effective for patients who cannot have surgery for their cancer.

Cetuximab belongs to a class of drugs called **targeted treatments**, which zero in on cell mechanisms that supply blood to tumors and promote their growth. Rather than killing both healthy and unhealthy cells, as chemotherapy does, targeted treatments attack cancer cells primarily, sparing healthy tissues and causing less severe side effects. Cetuximab works by blocking the **epidermal growth factor receptor (EGFR)**, one of the key substances that promote the growth of cancer cells. Even though many normal cells contain EGFRs, certain tumor cells, such as colorectal and head and neck tumors, contain excess amounts of them. In other words, the tumors **overexpress** EGFR. The more **receptors** on a cell, the more signals it receives to grow. Cetuximab prevents EGFR from starting this chain reaction that leads to cancer.

FOLFOX TREATMENT FOR ADVANCED COLORECTAL CANCER

New combinations of chemotherapy have been effective in treating people with advanced colorectal cancer after surgery. Doctors believe that perhaps the best of these treatments is a combination called **FOLFOX**. It consists of three drugs:

- 5-FU
- leucovorin (a form of the vitamin folic acid)
- oxaliplatin

Both during treatment and after, most people using this combination of drugs have fewer side effects than those using other combinations. And FOLFOX can prevent colorectal tumors from coming back. Studies now show that the benefits of using FOLFOX may last for more than five years.

An international clinical trial called MOSAIC evaluated more than 2,000 people with colorectal cancer who had surgery to

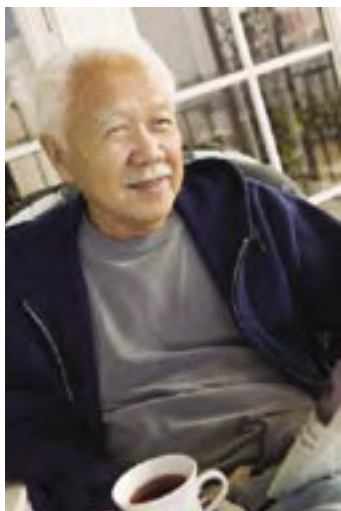
completely remove their tumors. Before joining the clinical trial, none of the participants had received any type of chemotherapy or radiation treatment. During the MOSAIC study, one group of patients was given FOLFOX. Another group was given the standard treatment, which consists of 5-FU and leucovorin.

People treated with FOLFOX lived longer before the cancer returned than those in the second group. This significant benefit of FOLFOX lasted as long as five years after treatment, especially in those who had advanced cancer. Nearly 75 percent of people with advanced colorectal cancer who were treated with FOLFOX were still alive six years after treatment, compared with only about 68 percent of those who received the standard treatment of 5-FU and leucovorin.

The beneficial effects of FOLFOX also seem to extend to people with colorectal cancer that has spread to the liver, according to the final results of a clinical trial from the European Organization for Research and Treatment of Cancer.

Colorectal cancer spreads to the liver in up to 50 percent of people diagnosed with this type of tumor. Even though tumors that spread to the liver are removed whenever possible, they often come back. For the first time, researchers found that FOLFOX given before and after surgery may lower the risk of the cancer returning to the liver.

In this clinical trial, approximately 350 people with metastatic colorectal cancer who were able to have surgery were assigned to one of two treatments. Half the patients received six cycles of FOLFOX to shrink the tumors before surgery and then six cycles after surgery. The other half had only the surgery. After about four years, the cancer did not come back in the



What's New, What's Important

- XELOX and FOLFOX produce similar results for people with metastatic colorectal cancer, so both are effective treatment options. Differences in side effects and in how the treatments are given (intravenous or oral) need to be considered.
- Chemotherapy-free intervals are not as effective as continuous maintenance chemotherapy for extending the lives of people with advanced colorectal cancer.

liver in about 40 percent of the people who had received chemotherapy, compared with about 30 percent of those who did not receive chemotherapy.

Researchers believe that this approach is effective. It may become one of the standards of care for people with colorectal cancer that has spread to the liver and can be surgically removed. But further studies are needed.

XELOX VERSUS FOLFOX FOR METASTATIC COLORECTAL CANCER

A comparison of FOLFOX, currently the standard treatment for metastatic colorectal cancer, and XELOX (capecitabine [Xeloda] and oxaliplatin) has been the subject of several recent clinical trials. All of the clinical trials reached the same conclusion: XELOX and FOLFOX produce similar results in terms of response to treatment and survival rates. Therefore, either one is an acceptable choice for treating advanced colorectal cancer.

Some side effects were more common with XELOX, and others were more common with FOLFOX. For instance, a skin reaction on the palms of the hands and feet called the hand-foot syndrome occurred more often with XELOX. On the other hand, **neutropenia**, a decrease in the number of white blood cells in the blood, occurred more often with FOLFOX. However, the fact that capecitabine can be taken by mouth at home is another consideration and may make XELOX more convenient for some patients.

The first study included more than 300 people with metastatic colorectal cancer at medical centers in France. About half of the patients received XELOX, and the other half received FOLFOX. Response was nearly identical with both treatments. The tumor shrank in about 45 percent of people in both groups.

An update of another international clinical trial based at the University of Glasgow, Scotland, focused on these two treatments. Originally, more than 600 patients were involved. They were divided into two groups: one group received

XELOX, and the other group received FOLFOX. Then, 1,400 people were added to the clinical trial to increase the numbers in each group. The researchers added bevacizumab (Avastin) to the treatment given to the XELOX group and to the FOLFOX group. Similar results were reported between the two groups. Members of both groups lived for about eight months without their cancer growing.

Yet another clinical trial from Vanderbilt-Ingram Cancer Center in Nashville, Tennessee, showed that XELOX and FOLFOX produced

similar results. This study included more than 600 people with metastatic colorectal cancer for whom treatment with irinotecan was not effective. Again, the time from the start of treatment until the cancer grew was the same for those who received XELOX and those who received FOLFOX—in this case, almost five months.

MAINTENANCE CHEMOTHERAPY VERSUS CHEMOTHERAPY-FREE INTERVALS FOR ADVANCED COLORECTAL CANCER

New combination treatments have improved survival for people with advanced colorectal cancer. But often these drugs

are associated with more serious side effects. Sometimes these side effects prevent people from completing their treatment. With this in mind, researchers based in France wanted to find out whether discontinuing chemotherapy after six cycles would have any effect on survival. Usually treatment includes continuing with “maintenance” chemotherapy after the initial cycles of treatment.

Called the OPTIMOX-2 clinical trial, this French study involved more than 200 people with advanced colorectal cancer. The people were split into two groups. One group received six cycles of chemotherapy with FOLFOX7, which includes the same drugs as standard FOLFOX treatment (oxaliplatin, leucovorin, and 5-FU) but a more intense dose of oxaliplatin. This was followed by maintenance chemotherapy with weekly doses of 5-FU and leucovorin. The other group was treated with six cycles of FOLFOX7 and no maintenance chemotherapy.

Those who received continuous maintenance chemotherapy lived longer than those who did not (25 months versus 19 months). So, even though a full break in chemotherapy offers quality-of-life advantages to people with advanced colorectal cancer, it cannot be recommended based on the results of this clinical trial.

It’s important to note that this clinical trial was performed before the targeted treatment bevacizumab was approved in France for advanced colorectal cancer. In an upcoming clinical trial, maintenance treatment with such targeted drugs alone will be evaluated in people with advanced colorectal cancer.

Please note: Although the treatments discussed in this chapter are showing promise, most are still in clinical trials—some in earlier phases of research—and may not be available yet to the general public. Your doctor can help guide you as to which new medications could be right for you and whether you are eligible to take part in the clinical trials of these new treatments.

