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HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ColorectalCancerUpdate.com** includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text.**

STATEMENT OF NEED/TARGET AUDIENCE

Colorectal cancer is among the most common cancers in the United States, and the arena of colorectal cancer treatment continues to evolve. Published results from ongoing clinical trials lead to the emergence of new therapeutic agents and regimens and changes in indications, doses and schedules for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances.

To bridge the gap between research and patient care, *Colorectal Cancer Update* utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME activity assists medical oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment.
- Counsel patients about the risks and benefits of adjuvant and neoadjuvant chemotherapy.
- Develop and explain a management strategy for patients with metastatic colorectal cancer.
- Describe ongoing clinical trials in colorectal cancer and counsel patients about the availability of ongoing clinical trials.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 5 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Hurwitz, Cassidy, and de Gramont on the integration of emerging clinical research data into the management of colorectal cancer.

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Herbert Hurwitz, MD

Grants/Research Support: Genentech BioOncology, GlaxoSmithKline, Pfizer Inc, Sanofi-Synthelabo Inc
Consultant and Honorarium: Genentech BioOncology

James Cassidy, MD, MBChB, MSc, FRCP

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Speakers Bureau: Roche Laboratories Inc, Sanofi-Synthelabo Inc

Aimery de Gramont, MD

Grants/Research Support: Baxter International Inc, Roche Laboratories Inc, Sanofi-Synthelabo Inc

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bevacizumab	Avastin™	Genentech BioOncology
capecitabine	Xeloda®	Roche Laboratories Inc
celecoxib	Celebrex®	Pfizer Inc
erlotinib	Tarceva®	Genentech BioOncology
fluorouracil (5-FU)	Various	Various
irinotecan	Camptosar®	Pfizer Inc
leucovorin calcium	Various	Various
oxaliplatin	Eloxatin®	Sanofi-Synthelabo Inc
paclitaxel	Taxol®	Bristol-Myers Squibb Company

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Editor's Note

Three tenors

By strange happenstance, during this year's ASCO meeting in New Orleans, I had the rare opportunity to interview three clinical investigators who recently presented clinical trial results that have permanently changed oncologic practice. On this program, Aimery de Gramont, Herbert Hurwitz and James Cassidy discuss the background, rationale, methods and initial findings of arguably the three most important Phase III clinical trial data sets in colorectal cancer treatment in more than a decade.

For over a year, I had attempted to arrange an interview with Aimery de Gramont. However, due to the length of our recording sessions and Dr de Gramont's relatively brief US visits, the time was never right for us to sit down and talk. Fortunately for our listeners, I was finally able to secure a time slot with the French researcher during the ASCO 2004 meeting. Unfortunately, as we began the discussion, the Louisiana skies opened and a spectacular thunderstorm ensued. When recording on location at meetings, we frequently confront aberrant noises such as sirens and train whistles. Usually, these can be edited out. In this case, though, the relentless booming and crackling are here to stay.

I actually like the dramatic audio accent the storm adds to our discussion of the MOSAIC trial, a landmark study that Dr de Gramont first presented at last year's ASCO meeting. The definitive paper on MOSAIC had just been published in the *New England Journal of Medicine* during the week I interviewed Dr de Gramont, and I was particularly interested in his reaction to Robert Mayer's accompanying editorial. As the clouds thundered outside, this very thoughtful investigator reviewed the clear-cut benefits associated with adjuvant FOLFOX in Stage III patients, and data his group had just reported that afternoon on its benefits in patients with higher-risk Stage II disease. The MOSAIC trial results have not only dramatically altered the nonprotocol approach to adjuvant systemic therapy, but also the design of subsequent adjuvant trials as evidenced by the many new randomized studies with variations of FOLFOX as the control arm.

Like Dr de Gramont, Herb Hurwitz is another busy trialist who is difficult to catch up with, and again I felt fortunate to meet with him in New Orleans. It is always amusing to conduct interviews at ASCO because everyone is frenzied with multiple simultaneous commitments. Dr Hurwitz — a very deep-thinking person who chooses words carefully — was able to take a deep breath and then calmly and concisely weave a fascinating research yarn.

The disappointments during Judah Folkman's angiogenesis chronicle have long preceded the bevacizumab story, and for years many believed that anti-angiogenic treatment would not play out clinically. This perception was reinforced in December 2002 at the San Antonio Breast Cancer Symposium when Kathy Miller presented the disappointing results from the randomized trial that added "bev" to capecitabine in women with previously treated metastatic breast cancer. I had been chatting with Kathy for some time as that critical study accrued and then finally reported results, and when we sat down for an interview, it was obvious she was disappointed, but hopeful that another ongoing first-line ECOG trial of bev plus paclitaxel as first-line therapy in women with metastatic breast cancer would be positive.

After that inauspicious anti-VEGF debut in December 2002, all hell broke loose at the ASCO 2003 meeting. Soft-spoken Herb calmly presented a biologic blockbuster — bevacizumab added more to IFL in terms of progression-free and overall survival than the addition of irinotecan to 5-FU and leucovorin, which led to the IFL FDA indication.

With these now landmark results, which were published with MOSAIC in the June 3rd issue of the *New England Journal of Medicine*, the Folkman anti-angiogenesis legacy is clearly alive. Or is it? Researchers like Lee Ellis have postulated that the benefits encountered with bevacizumab were actually related to the *normalization* of the vasculature within tumors, allowing for greater penetration of cytotoxic agents, rather than *cutting off* the blood supply. Who knows? The bottom line is that more patients are staying alive and feeling better, and adjuvant bevacizumab trials are on their way.

The final member of the memorable investigator trio appearing on this program, James Cassidy, met with me shortly after presenting perhaps the most anticipated GI research report at the 2004 ASCO meeting, the initial results from the X-ACT trial demonstrating at least equivalence in tumor control for capecitabine compared to the Mayo Clinic regimen of 5-FU and leucovorin as adjuvant therapy. Not only does this study obviate the need for a commonly utilized but inconvenient parenteral regimen, but for the first time, we have clinical trial evidence that capecitabine is much more than oral 5-FU. The original objective of this study was to demonstrate equivalence in efficacy with improved tolerability and convenience. X-ACT surprised even Dr Cassidy with tantalizing relapse-free and overall survival advantage for capecitabine, although only RFS was statistically significant. Perhaps the promise of intratumoral prodrug-activation via thymidine phosphorylase has now truly been fulfilled. In any event, patients have one more effective, relatively nontoxic alternative as adjuvant therapy.

I always feel privileged to have the opportunity to chat with the great minds in our field, but it was particularly striking to have the chance to listen to these three humble but visionary research leaders. After years of inertia in the treatment of this very important cancer, the work of these and other investigators is rapidly altering the colorectal cancer treatment landscape.

— Neil Love, MD
NLove@ResearchToPractice.net

Phase III trial of IFL with or without bevacizumab

Trial background

In the initial Phase I studies of bevacizumab, very minimal toxicity and favorable pharmacokinetics were observed — as expected for a monoclonal antibody. The Phase II studies of bevacizumab in conjunction with 5-FU/leucovorin showed a remarkably higher response rate, time to progression and a trend for improvement in survival than 5-FU/leucovorin alone (1.1).

A study reported by Fairooz Kabbinavar in the *Journal of Clinical Oncology* demonstrated that adding bevacizumab, which had a relatively modest safety profile, to 5-FU/leucovorin accounted for a marked increase in clinical activity.

1.1 Phase II Randomized Trial Comparing Bevacizumab Plus 5-FU/LV with 5-FU/LV Alone in Patients with Previously Untreated Metastatic Colorectal Cancer

	5-FU/LV (n=36)	5-FU/LV + bevacizumab 5 mg/kg (n=35)	5-FU/LV + bevacizumab 10 mg/kg (n=33)
Objective response rate	17%	40%	24%
Time to progression	5.2 mo	9.0 mo	7.2 mo
Median survival	13.8 mo	21.5 mo	16.1 mo

"These preliminary results suggest that bevacizumab, in combination with FU/LV, increases response rate, prolongs time to progression, and prolongs survival compared with FU/LV alone in patients with metastatic colorectal cancer. ..."

SOURCE: Kabbinavar F et al. **Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21:60-5. **Abstract**

Dr Hurwitz is an Associate Professor of Medicine in the Division of Hematology/Oncology, Clinical Director of the Phase I Program, and Co-leader of the GI Oncology Program at Duke University Medical Center in Durham, North Carolina.

During the design of the current Phase III study, the standard of care for colorectal cancer in the United States had just evolved once more from 5-FU/leucovorin to bolus IFL, also known as the Saltz regimen.

That's why our study initially had three arms: IFL plus placebo, IFL plus bevacizumab, and 5-FU/leucovorin plus bevacizumab. Safety data were not available at that time for the four-drug combination of IFL plus bevacizumab.

We allowed approximately 100 patients to be randomly assigned to each of the three arms and then evaluated the toxicity of each regimen. When the Data Safety Monitoring Committee noted no excess toxicity when bevacizumab was added to IFL, the 5-FU/leucovorin arm was discontinued as prespecified in the protocol. This study was designed essentially to compare a regimen including bevacizumab to the standard of care.

The primary question in our study was: What is the value of adding bevacizumab to IFL? The "clinical trial gods" like simple questions, and our study asked a simple question, was well conducted and had clean results.

Efficacy

The trial involved 923 patients, randomly assigned to IFL or to IFL plus bevacizumab. The patients on the IFL-alone arm had a median survival of 15.6 months, which corresponds to the reports of IFL by Saltz and others. The survival with IFL plus bevacizumab was 20.3 months, which importantly breaks the 20-month barrier (1.2).

Patients' risk of dying was reduced by approximately one third, which was highly statistically significant. We also saw improvements in time to progression and response rate. The response rate went from approximately 35 percent to 45 percent, which was also highly statistically significant.

The 5-FU/leucovorin plus bevacizumab arm is nicknamed "chemo-light" plus bevacizumab, and it's particularly intriguing. That regimen has remarkable activity. While the results were not statistically significant, an interesting trend was observed with respect to response rate, time to progression and overall survival when comparing all three arms of the study.

In general, the least efficacious regimen was IFL, followed by 5-FU/leucovorin plus bevacizumab and the four-drug combination of IFL plus bevacizumab. The four-drug combination appears to be best at all points, but it's remarkable that the 5-FU/leucovorin/bevacizumab — the "chemo-light" plus bevacizumab regimen — benchmarks reasonably well compared to IFL.

Three data sets demonstrate the activity of the 5-FU/leucovorin/bevacizumab regimen: the initial randomized Phase II study reported by Fairooz Kabbinavar, arm 3 of our study with 100 patients and the study reported by Kabbinavar at ASCO this year involving more than 200 patients, again demonstrating that 5-FU/leucovorin plus bevacizumab outperforms 5-FU/leucovorin alone.

1.2 Phase III Randomized Trial of IFL with or without Bevacizumab for Patients with Previously Untreated Metastatic Colorectal Cancer

	IFL/placebo (n=411)	IFL/BV (n=402)	*p*-value
Median survival	15.6 months	20.3 months	<0.001
One-year survival	63.4%	74.3%	<0.001
Progression-free survival	6.2 months	10.6 months	<0.001
Overall response rate Complete response Partial response	34.8% 2.2% 32.6%	44.8% 3.7% 41.0%	0.004
Median duration of response	7.1 months	10.4 months	0.001

Bevacizumab = 5 mg/kg every two weeks

SOURCE: Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Side effects and tolerability

The side-effect profile for bevacizumab was remarkably benign. In general, we saw IFL-related side effects in both arms of the study, as would be expected. Bevacizumab resulted in a slight increase in the total number of Grade III or Grade IV toxicities from approximately 75 to 80 percent. Most of these were Grade III and manageable. Very few additional side effects were noted, and there was no increase in side effects leading to death on study or 60-day all cause mortality (1.3).

Traditional chemotherapy-related side effects, including nausea, vomiting, diarrhea and leukopenia, were essentially the same in both arms of the study. Certain bevacizumab-related side effects were specifically evaluated as part of the study, and we did not see an increase in thrombosis, bleeding or proteinuria. This is probably related to the fact that patients with metastatic colorectal cancer treated with intense chemotherapy are prone to these problems at baseline.

One of the most attractive features of the randomized placebo-controlled design of our study is that we were not only able to have a better evaluation of efficacy, but particularly a better evaluation of the real safety profile for bevacizumab.

We noted mild, clinically insignificant hypertension in about one fourth of patients receiving bevacizumab, and about 11 percent of patients experienced increased blood pressure requiring the addition of an oral antihypertensive. However, no patient experienced a hypertensive crisis, and many antihypertensive agents have been used successfully to manage the hypertension when it occurs.

Gastrointestinal (GI) perforations were an unexpected problem in the bevacizumab arm. These events have a presentation similar to that of severe bowel syndrome (perforation and fistula formation) and have been observed in two to three percent of patients with metastatic colorectal cancer treated with a 5-FU-based regimen.

Patients with GI perforations had variable presentations, sometimes in the setting of tumor response or during a colonoscopy to sort out another complication. GI perforations may have been related to injuries to the bowel caused by chemotherapy side effects. With only six events out of 400 patients (all in the IFL plus bevacizumab arm), it's very difficult to identify the true predisposing factors.

Of the patients with GI perforations, one died, two had to discontinue treatment permanently, and three restarted therapy after they recovered and experienced no subsequent sequelae. I think the important message is that larger data sets will more clearly identify the predisposing factors, and that studies to address this issue are ongoing. Another important message is that GI perforations are relatively rare, and many patients recover — and an overall survival benefit is associated with bevacizumab.

1.3 IFL versus IFL/Bevacizumab: Selected Adverse Events*

Adverse event	IFL/placebo (n=397)	IFL/BV (n=393)
Any Grade III/IV event	294 (74.0%)	334 (84.9%†)
Grade III/IV leukopenia	123 (31.1%)	145 (37.0%)
Grade III/IV diarrhea	98 (24.7%)	127 (32.4%)
Grade III/IV bleeding	10 (2.5%)	12 (3.1%)
Grade III hypertension	9 (2.3%)	43 (11.0%†)
Grade III proteinuria	3 (0.8%)	3 (0.8%)
Any thrombotic event	64 (16.2%)	76 (19.4%)
Deep thrombophlebitis	25 (6.3%)	35 (8.9%)
Pulmonary embolus	20 (5.1%)	14 (3.6%)
Event requiring hospitalization	157 (39.6%)	177 (44.9%)
Event leading to death	11 (2.8%)	10 (2.6%)
60-day all cause mortality	19 (4.9%)	12 (3.0%)
Gastrointestinal perforation	0 (0.0%)	6 (1.5%)

*Not adjusted for differences in the median duration of therapy between IFL and IFL/bevacizumab groups (27.6 weeks versus 40.4 weeks).

† $p < 0.01$

SOURCE: Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Select publications

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Kabbinavar F et al. **Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21(1):60-5. **Abstract**

Mass RD et al. **Bevacizumab in combination with 5-FU/leucovorin improves survival in patients with metastatic colorectal cancer: A combined analysis.** *Proc ASCO* 2004;**Abstract 3616**.

James Cassidy, MD, MBChB, MSc, FRCP

EDITED COMMENTS

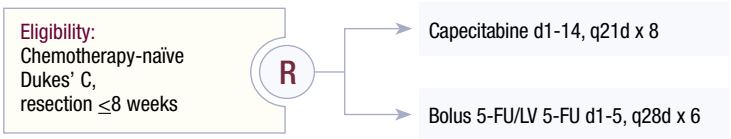
The Xeloda® in Adjuvant Colon Cancer Therapy trial

Trial design

In the Xeloda® in Adjuvant Colon Cancer Therapy (X-ACT) trial, the Mayo Clinic regimen was chosen as the standard treatment because: (1) it was the predominant schedule used in North America, (2) it was the regimen preferred by the FDA as a comparator, and (3) analyses conducted in European countries indicated that the bolus regimen was still frequently used. Capecitabine was selected as the other treatment. Approximately 2,000 patients with Dukes' C colon cancer were randomly assigned within eight weeks of their surgery to the six courses of Mayo Clinic regimen or eight courses of capecitabine (2.1).

2.1 X-ACT Study: Randomized Phase III Adjuvant Trial Comparing Capecitabine to Bolus 5-FU/Leucovorin in Patients with Dukes' C Colon Cancer

Protocol ID: X-ACT
Accrual: 1,987 (Closed)



SOURCES: Cassidy J et al. *Proc ASCO* 2004;**Abstract 3509**. Cassidy J on behalf of the X-ACT investigators. Presentation. *ASCO* 2004.

Demographics

Patients over the age of 75 were not permitted in the original protocol; however, a number of protocol waivers allowed patients older than 75 years to be entered into the trial. The age range of the patients in the trial reflects a disease that

Dr Cassidy is a Professor of Oncology and Head of the Department of Cancer Research in the UK Department of Medical Oncology at the University of Glasgow in Glasgow, Scotland.

occurs predominantly in patients in their sixties and seventies. Our data are comparable to data from any other clinical trial. We've deliberately analyzed what happens to older patients within the protocol, and no toxicity or efficacy disadvantages are associated with patients older than 75 years.

Efficacy

The trial was powered to show equivalence in the primary endpoint — disease-free survival (DFS). A number of secondary endpoints were relapse-free survival (RFS), overall survival (OS), pharmacoeconomics and quality of life. The patients in the X-ACT trial have been followed for a median of 3.8 years. In terms of the primary endpoint of DFS, the trial demonstrated equivalence between the two treatments.

A statistically significant difference was observed in RFS; fewer patients treated with capecitabine experienced a relapse in their disease. Overall survival was also improved for patients treated with capecitabine, but it was not a statistically significant improvement. Because the trial did not include many patients yet at risk for death, we must wait to determine the precise answer about the difference in OS. In conclusion, capecitabine is at least equivalent to the Mayo Clinic regimen and probably better.

Toxicity

Capecitabine was less toxic than the Mayo Clinic regimen in terms of diarrhea, mucositis, neutropenia and neutropenic sepsis. However, more patients treated with capecitabine developed hand-foot syndrome, which is a nuisance and requires dose reductions but is not life threatening. In my opinion, hand-foot syndrome is quite low in rank order of importance. The treatment-related mortality rates were 0.3 percent with capecitabine and 0.4 percent with the Mayo Clinic regimen. The treatment-related deaths were due to a combination of diarrhea and neutropenia. Compared to other adjuvant trials reported in the literature, that mortality rate was lower in the X-ACT trial.

Over 80 percent of the patients in both arms received the full duration of therapy. Just over half of the patients in both arms required a dose reduction, delay or interruption. With capecitabine we have the potential to interrupt the dosing, and patients and caregivers must be involved in that process.

Educating patients about capecitabine-associated side effects

We make an effort to educate patients about the potential for diarrhea because if patients develop diarrhea, they may become dehydrated and require hospitalization. Sometimes diarrhea is associated with neutropenia. Diarrhea and neutropenia together are dreaded side effects of the fluoropyrimidines. Patients must be admitted to the hospital to receive broad-spectrum antibiotics and rehydration. I tell my patients they should stop treatment and inform us if they are having diarrhea more than five times in a 24-hour period.

Hand-foot syndrome is a bit more subtle. Patients often develop a minor degree of hand-foot syndrome with the first cycle of capecitabine, and it may be worse

with the second cycle. At that point, we reduce the capecitabine dose. Because of that strategy, I don't see many patients with severe hand-foot syndrome. We also tell patients to stop treatment if they develop redness of their hands or feet with pain that interrupts their level of functioning.

CALGB-89803: Adjuvant trial comparing IFL to bolus 5-FU/leucovorin

CALGB-89803 compared IFL to the Roswell Park bolus 5-FU/leucovorin regimen. The Roswell Park regimen is probably equivalent to the Mayo Clinic regimen and may be less toxic. It was a resoundingly negative trial; no differences between the two treatments were found. It has been questioned whether the early deaths encountered with the IFL regimen were sufficient to have negated any possible benefit. The results were unexpected. In patients with advanced disease, IFL seems to be a better regimen than 5-FU/leucovorin; hence, it's counterintuitive to not have a positive study in the adjuvant setting.

Adjuvant therapy options for patients with Stage III disease

Adjuvant therapy options include the Mayo Clinic regimen, capecitabine or the addition of oxaliplatin to 5-FU/leucovorin (FOLFOX). Based on the X-ACT trial results, the standard of care may deviate from the Mayo Clinic regimen towards single-agent capecitabine. For me, it's a done deal. Others may say, "It's only one trial. We need more data."

Recent trials evaluating celecoxib with chemotherapy

Interesting results from trials evaluating celecoxib in combination with chemotherapy were reported at ASCO 2004. In one trial, celecoxib's ability to reduce the incidence of oxaliplatin-related neurotoxicity was tested. Concurrent use of celecoxib and oxaliplatin appears to cause less neurotoxicity. In another clinical trial from the French group conducting the OPTIMOX study, in which oxaliplatin is administered, stopped and then reintroduced, that strategy was administered concurrently with celecoxib and the response rates were lower than the response rates historically seen in the OPTIMOX study. I wonder whether a pharmacokinetic or pharmacodynamic interaction between celecoxib and oxaliplatin reduces the activity and toxicity of oxaliplatin.

Researchers from MD Anderson reported trial results suggesting that celecoxib in combination with capecitabine might cause less hand-foot syndrome. I would like to see that evaluated in a larger, more formal trial. I'd also want to ascertain that a reduction in the activity of capecitabine didn't occur along with the reduction in the incidence of hand-foot syndrome.

Educating patients about oxaliplatin-related neurotoxicity

We have a discussion with patients about short-term neurotoxicity, such as laryngopharyngeal dysesthesia, because it's quite frightening. If they are not told that it can happen, they become scared when the symptoms occur. Then, some patients may not want to be treated with a second cycle.

If they are educated in advance, they cope with it. In terms of the long-term cumulative neuropathy, we ask: Do you have neuropathy that is persistent between cycles? Does the neuropathy have a functional consequence? If the answer is yes to either of those two questions, then we'll reduce the oxaliplatin dose.

Select publications

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Agafitei RD et al. **Effect of celecoxib on neurotoxicity in patients with metastatic colorectal cancer treated with 5-FU/oxaliplatin (CIFOX).** *Proc ASCO* 2004;**Abstract 3600**.

Andre T et al. **Phase II study of an optimized 5FU-oxaliplatin strategy (OPTIMOX2) with celecoxib in metastatic colorectal cancer: A GERCOR study.** *Proc ASCO* 2004;**Abstract 3554**.

Arkenau HT et al. **Phase III trial of infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus capecitabine plus oxaliplatin (CAPOX) as first line treatment in advanced colorectal carcinoma (ACRC): Results of an interim safety analysis.** *Proc ASCO* 2004;**Abstract 3546**.

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Aimery de Gramont, MD

EDITED COMMENTS

MOSAIC adjuvant trial

Rationale

Two clinical trials, one in the advanced disease setting and the other in the adjuvant setting, provided the rationale for the MOSAIC adjuvant trial. The trial in patients with advanced disease, published in the *Journal of Clinical Oncology* in 2000, compared a bimonthly regimen of 5-FU/leucovorin (leucovorin plus bolus and infusional 5-FU administered for two days) with or without oxaliplatin.

Patients treated with oxaliplatin plus bimonthly 5-FU/leucovorin (FOLFOX) had a response rate of 50 percent, which was more than double the response rate for the patients treated with bimonthly 5-FU/leucovorin alone. Patients receiving FOLFOX had a progression-free survival of almost nine months, again very different from the patients treated with bimonthly 5-FU/leucovorin alone.

The adjuvant trial compared a monthly five-day bolus 5-FU/leucovorin regimen to the bimonthly bolus and infusional 5-FU/leucovorin regimen. The results from that adjuvant trial, published in the *Journal of Clinical Oncology* in 2003, demonstrated similar efficacy, but less toxicity for the bimonthly 5-FU/leucovorin regimen.

Efficacy

The MOSAIC adjuvant trial was conducted worldwide and involved 2,246 patients with Stage II or III disease who were less than 75 years of age. Because it was too early to analyze overall survival, a difference was not found at three years. We have published the three-year disease-free survival results demonstrating a significant five percent improvement for patients treated with adjuvant FOLFOX (3.1).

When the subsets of the population (ie, patients with Stage II or III disease and all other prognostic factors) were analyzed, all groups of patients benefited from adjuvant FOLFOX. In the patients with Stage III disease, the absolute difference in disease-free survival was approximately seven percent, which equated to a 23 percent reduction in the risk of recurrence. In patients with Stage II disease, the absolute difference in disease-free survival was 2.7 percent, which equated to a

Dr de Gramont is a Professor of Oncology (Professeur des Universités-Praticien Hospitalier) and the Department Head of Internal Medicine in Oncology at the Hôpital Saint-Antoine in Paris, France.

20 percent reduction in the risk of recurrence. Clearly, patients with higher-risk disease benefit more from adjuvant FOLFOX, but we cannot say that patients with Stage II disease do not benefit.

At ASCO 2004, we presented data from the patients with Stage II disease enrolled in the MOSAIC adjuvant trial. In an analysis of the patients with high-risk Stage II disease (eg, T4, bowel obstruction, tumor perforation, venous invasion or less than 10 lymph nodes analyzed), the difference in disease-free survival in favor of FOLFOX was more than five percent. In patients with high-risk Stage II disease, adjuvant FOLFOX should be considered.

3.1 MOSAIC Trial: Estimated Three-Year Disease-Free Survival for Adjuvant Chemotherapy

	FOLFOX	FL	Hazard ratio
Overall[1] (n=1,123 / 1,123)	78.2%	72.9%	0.77 [0.65-0.91], $p = 0.002$
Stage III[1] (n=672 / 675)	72.2%	65.3%	0.76 [0.62-0.92]
Stage II[1] (n=451 / 448)	87.0%	84.3%	0.80 [0.56-1.15]
High-Risk* Stage II[2] (n=286 / 290)	84.9%	79.8%	0.72 [0.48-1.08]

FL = (leucovorin 2-hour infusion + 5-FU bolus and 22-hour continuous infusion) days 1-2 every 2 weeks for 6 months. FOLFOX = (FL + oxaliplatin day 1) every 2 weeks x 6 months.

*T4, bowel obstruction, tumor perforation, poorly differentiated tumor, venous invasion or number of examined lymph nodes <10.

SOURCES: [1]André T et al for the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. **Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.** *N Engl J Med* 2004;350(23):2343-51. **Abstract**

[2]Hickish T et al. **FOLFOX4 as adjuvant treatment for stage II colon cancer (CC): Subpopulation data from the MOSAIC trial.** Presentation. *ASCO* 2004. **Abstract**

The first update to the MOSAIC trial, with almost four years of follow-up, will be presented at the 2004 European Society for Medical Oncology (ESMO) meeting. I am not sure why, but we have observed that the results appear to be improving. In one or two years, we may have the first results of overall survival.

Toxicity

The overall safety in the MOSAIC adjuvant trial was good. No excess deaths occurred with FOLFOX compared to 5-FU/leucovorin alone. We did observe more GI toxicity with FOLFOX, but the differences in the incidence of the toxicities remained low. The two main toxicities associated with oxaliplatin were neutropenia and sensory peripheral neuropathy. Grade III or IV neutropenia occurred in 41 percent of the patients treated with FOLFOX. Because it is a bimonthly regimen, the patients' blood counts were always at their nadir; however, only about two percent of the patients treated with FOLFOX had febrile neutropenia.

Grade III sensory peripheral neuropathy, which indicates some degree of functional impairment, occurred in 12 percent of the patients receiving FOLFOX. With follow-up, this neuropathy was reversible. Grade II or III neuropathy remained in only six percent of the patients after one-year of follow-up and in 3.9 percent of the patients at 18 months of follow-up.

Three-year disease-free survival as an endpoint for adjuvant colon cancer trials

At ASCO 2004, Dan Sargent presented data demonstrating that a very strong correlation exists between three-year disease-free survival and five-year overall survival. Hence, we don't need to wait an additional two years to determine whether one adjuvant treatment is better than another if the differences in the three-year disease-free survival are large, like in the MOSAIC study. Waiting for five-year overall survival means not treating some patients who could potentially avoid relapse.

Clearly, it's important to have an early endpoint. The FDA has also decided to recognize three-year disease-free survival as an endpoint for adjuvant studies, not only because of the correlation between three-year disease-free survival and five-year overall survival, but also because not relapsing is a good quality-of-life endpoint.

Adjuvant therapy for patients not enrolled in a clinical trial

I would certainly offer adjuvant FOLFOX to patients with Stage III or high-risk Stage II disease, and I would discuss it with the other patients. In patients with a very good prognosis, the potential risks and benefits of an adjuvant regimen must be weighed in a discussion that should occur between the patient and physician.

In patients with low-risk Stage II disease, the benefit of an adjuvant regimen without oxaliplatin (eg, 5-FU/leucovorin) is about two percent. If an additional two percent benefit can be obtained with the addition of oxaliplatin, then a four percent benefit can be considered. A well-informed patient can decide whether an increase in survival of a few percent is worth the risk of developing neuropathy.

OPTIMOX trials

Oxaliplatin is usually discontinued in therapy of metastatic disease because of neuropathy, not tumor progression. It's important to maintain sensitivity to oxaliplatin to optimize its use. We have experience with the reintroduction of oxaliplatin in the OPTIMOX trials.

The OPTIMOX-I trial compared FOLFOX4 administered until disease progression to six cycles of FOLFOX7, with a higher dose of oxaliplatin, followed by maintenance therapy with 5-FU/leucovorin alone for six months and later reintroduction of FOLFOX7. Median overall survival was 20.7 months for the patients receiving FOLFOX4 and 21.4 months for the patients receiving FOLFOX7, which was not a significant difference.

Dose-intense oxaliplatin did not improve the response rate or resection rate, but patients receiving only six cycles had fewer side effects. A strategy that allows the reintroduction of oxaliplatin (eg, second-line therapy with the same regimen used as first-line therapy) and the subsequent utilization of an irinotecan-based regimen may increase survival.

In the OPTIMOX-II trial, we evaluated a strategy involving FOLFOX7 for six cycles, stopping all chemotherapy and then reintroducing FOLFOX7 before the tumor reached its baseline measure. The OPTIMOX-III trial will compare capecitabine and oxaliplatin (XELOX) plus FOLFOX for three months with or without erlotinib during the break in chemotherapy.

Select Publications

André T et al. **Phase II study of an optimized 5FU-oxaliplatin strategy (OPTIMOX2) with celecoxib in metastatic colorectal cancer: A GERCOR study.** *Proc ASCO* 2004;**Abstract 3554**.

André T et al; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. **Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.** *N Engl J Med* 2004;350(23):2343-51. **Abstract**

André T et al. **Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: Results of a randomized trial.** *J Clin Oncol* 2003;21(15):2896-903. **Abstract**

Cunningham D et al. **Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.** *N Engl J Med* 2004;351(4):337-45. **Abstract**

de Gramont A et al. **Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer.** *J Clin Oncol* 2000;18(16):2938-47. **Abstract**

de Gramont A et al. **OPTIMOX study: FOLFOX 7/LV5FU2 compared to FOLFOX 4 in patients with advanced colorectal cancer.** *Proc ASCO* 2004;**Abstract 3525**.

de Gramont A et al. **Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French intergroup study.** *J Clin Oncol* 1997;15(2):808-15. **Abstract**

Giantonio BJ et al. **The addition of bevacizumab (anti-VEGF) to FOLFOX4 in previously treated advanced colorectal cancer (advCRC): An updated interim toxicity analysis of the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO GI Cancer Symposium* 2003;**Abstract 241**.

Hickish T et al. **FOLFOX4 as adjuvant treatment for stage II colon cancer (CC): Subpopulation data from the MOSAIC trial.** *Proc ASCO* 2004;**Abstract 3619**.

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Mabro M et al. **Irinotecan, 5-fluorouracil infusion and leucovorin, (FOLFIRI-3) in pretreated patients with metastatic colorectal cancer: Results of a multicenter phase II study.** *Proc ASCO* 2003;**Abstract 1125**.

Sargent DJ et al. **Disease-free survival (DFS) vs. overall survival (OS) as a primary endpoint for adjuvant colon cancer studies: Individual patient data from 12,915 patients on 15 randomized trials.** *Proc ASCO* 2004;**Abstract 3502**.

Scheithauer W et al. **Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer.** *J Clin Oncol* 2003;21(7):1307-12. **Abstract**

Post-test:
Colorectal Cancer Update — Issue 5, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In the Phase III randomized trial of IFL with or without bevacizumab for patients with previously untreated metastatic colorectal cancer, the addition of bevacizumab resulted in significantly more:
   a. Proteinuria
   b. Hypertension
   c. Thromboembolic events
   d. All of the above

2. IFL plus bevacizumab resulted in significant improvements compared to IFL alone in which of the following efficacy endpoints?
   a. Median survival
   b. Progression-free survival
   c. Overall response rate
   d. Median duration of response
   e. All of the above

3. In the X-ACT adjuvant trial, the Mayo Clinic regimen was superior to capecitabine in terms of disease-free survival.
   a. True
   b. False

4. In the X-ACT trial, which of the following side effects were more commonly associated with capecitabine?
   a. Diarrhea
   b. Hand-foot syndrome
   c. Mucositis
   d. Neutropenia

5. In the CALGB adjuvant trial comparing IFL to bolus 5-FU/leucovorin, IFL was found to be superior in terms of disease-free survival and overall survival.
   a. True
   b. False

6. Celecoxib may reduce the incidence of toxicities associated with:
   a. Capecitabine
   b. Oxaliplatin
   c. Bevacizumab
   d. Both a and b
   e. All of the above

7. In the MOSAIC adjuvant trial, patients treated with FOLFOX had:
   a. An improvement in three-year disease-free survival
   b. An improvement in overall survival
   c. An increase in the number of treatment-related deaths
   d. Both a and b
   e. All of the above

8. In an analysis of the patients with high-risk Stage II disease who were enrolled in the MOSAIC adjuvant trial, the absolute difference in disease-free survival in favor of FOLFOX was more than five percent.
   a. True
   b. False

9. The OPTIMOX-I trial evaluated which of the following regimens:
   a. FOLFOX4 administered until disease progression
   b. FOLFIRI3
   c. Six cycles of FOLFOX7 → maintenance 5-FU/leucovorin for six months → reintroduction of FOLFOX7
   d. Both a and b
   e. Both a and c

10. Which of the following statements about FOLFIRI3 is incorrect?
    a. It has a response rate of 20 percent in patients previously treated with FOLFOX
    b. It utilizes a split dose of oxaliplatin
    c. It utilizes a split dose of irinotecan
    d. Both a and b
    e. Both b and c

11. In the MOSAIC adjuvant trial, the FOLFOX regimen resulted in 12% Grade III sensory peripheral neuropathy, which was irreversible.
    a. True
    b. False

Post-test Answer Key: 1b, 2e, 3b, 4b, 5b, 6d, 7a, 8a, 9e, 10b, 11b

Evaluation Form:
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Please answer the following questions by circling the appropriate rating:

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	N/A = not applicable to this issue of *CCU*

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *CCU* address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment. . . . . 5 4 3 2 1 N/A
- Counsel patients about the risks and benefits of adjuvant and neoadjuvant chemotherapy. . . . . 5 4 3 2 1 N/A
- Develop and explain a management strategy for patients with metastatic colorectal cancer. . . . . 5 4 3 2 1 N/A
- Describe ongoing clinical trials in colorectal cancer and counsel patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Herbert Hurwitz, MD	5 4 3 2 1	5 4 3 2 1
James Cassidy, MD, MBChB, MSc, FRCP	5 4 3 2 1	5 4 3 2 1
Aimery de Gramont, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1
Related to my practice needs. 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Evaluation Form:
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FOLLOW-UP

As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

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