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Colorectal Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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Colorectal Cancer Update
A CME Audio Series and Activity

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

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment, and incorporate these data into management strategies in the local and advanced disease settings.
- Counsel appropriate patients about the availability of ongoing clinical trials.
- Evaluate the emerging research data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients.
- Evaluate emerging research data on various neoadjuvant radiation therapy/chemotherapy approaches to rectal cancer and explain the absolute risks and benefits of these regimens to patients.
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 2 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Tepper, Hecht and Tabernero on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

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 CME activity with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **blue underlined text**.

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HELP US EVALUATE A NEW PATIENT EDUCATION TOOL

Research To Practice has recently launched a pilot education program for patients dealing with issues specific to adjuvant systemic therapy of colorectal cancer. We are currently recruiting patients with colorectal cancer to evaluate this integrated audio, web and text-based initiative.

To recommend patients for participation or for more information, please contact: **NLove@ResearchToPractice.net**.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Tepper — Consulting Fees: Genentech BioOncology. **Dr Hecht** — Consulting Fees: Amgen Inc, Novartis Pharmaceuticals, OSI Pharmaceuticals; Contracted Research: Amgen Inc, Genentech BioOncology, Novartis Pharmaceuticals, OSI Pharmaceuticals; Ownership Interest: Amgen Inc. **Dr Tabernero** — Consulting Fees: Merck KGaA, Sanofi-Aventis; Contracted Research: Merck KGaA.

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UPCOMING EDUCATIONAL EVENTS

NSABP Group Meeting
April 28-May 1, 2006
Denver, Colorado
Event website: **www.nsabp.pitt.edu**

2006 ASCO Annual Meeting
June 2-6, 2006
Atlanta, Georgia
Event website: **www.asco.org**

American College of Surgeons Oncology Group (ACOSOG) Semiannual Meeting
June 22-24, 2006
Chicago, Illinois
Event website: **www.acosog.org**

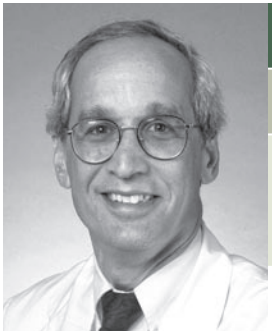
RTOG Semiannual Meeting
June 22-25, 2006
Toronto, Ontario
Event website: **www.rtog.org**

ECOG Semiannual Meeting
June 23-25, 2006
Washington, DC
Event website: **www.ecog.org**

UICC World Cancer Congress 2006
July 8-12, 2006
Washington, DC
Event website: **www.worldcancercongress.org**

2nd Annual Oncology Congress
October 19-21, 2006
New York, New York
Event website: **www.oncologycongress.com**

48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology
November 5-9, 2006
Philadelphia, Pennsylvania
Event website: **www.astro.org**



INTERVIEW

Joel Tepper, MD

Dr Tepper is Professor and Chair in the Department of Radiation Oncology at University of North Carolina School of Medicine in Chapel Hill, North Carolina.

CD 1, Tracks 1-16

Select Excerpts from the Interview

CD 1, Tracks 3-4

DR LOVE: What have we learned over the past couple of years about staging rectal cancer?

DR TEPPER: First of all, I want to emphasize that we are in an age driven by molecular biology and elaborate ways of evaluating disease. However, what we have found is that some very standard, straightforward factors can make a real difference in terms of understanding the risks and outcomes of the disease. We

need to emphasize the importance of what goes on both surgically and pathologically with the disease and how we interpret these data.

A series of articles has been published that has taken the lead in examining the impact of T stage and N stage on outcome for patients with rectal cancer (Gunderson 2002, 2004). It's been known for years that N stage is important. In fact, many treatment algorithms for rectal cancer are based almost entirely on the premise that N stage dominates everything in terms of outcome.

However, the data from these studies show that both the T stage and the N stage of the tumor are important, and the impact of each on disease outcome is somewhat independent of the other. If you look at the data carefully, it is evident that someone with T2/N1 disease might have a slightly better prognosis than someone who has T3/N0 disease.

In a patient with N0 disease or, perhaps, N1 disease, the T stage is significant in determining the risk for both local and distant recurrence. So T stage has a big impact on survival differences, far larger than any impact that results from a therapeutic intervention additive to surgery, such as chemotherapy, radiation therapy, or a combination of the two.

In a study published several years ago, we evaluated tissue from patients with rectal cancer in terms of T and N staging (Tepper 2001). The study was based on an analysis of patients from the Gastrointestinal (GI) Intergroup study 0114, in which all patients with rectal cancer were treated postoperatively with chemotherapy and radiation/chemotherapy and then more chemotherapy. No difference appeared between the therapeutic interventions, so we were able to combine all of the treatment categories together.

When we looked at the data, we found that the number of lymph nodes examined had a great impact on outcome. More specifically, among patients with T3/N0 disease, the outcome was far worse if the pathologist found zero to eight nodes compared to finding 14 or more nodes in the specimen. Again, this difference was much bigger than the differences we see among therapeutic interventions.

This suggests to me the extreme importance of how we select patients who are at high risk, both in terms of how we define the outcomes of studies as well as how we define whom we should and shouldn't treat with adjuvant therapies. For example, it is possible that a patient with T3/N0 disease, which has been well staged with many nodes that are negative, may not need adjuvant therapy, or at least not the same level of adjuvant therapy as he or she would need otherwise.

Another issue is whether nodal pathology outcomes are related to the surgeon's skill and how well the operation was performed or to how well and how carefully the pathologist examined the specimen. We can't answer this question definitively from this study, but the data suggest that the pathologist had a greater effect on outcomes than the surgeon. This is based on the fact that the number of nodes the pathologist found appeared to have a large effect on outcome for the patients with T3/N0 disease.

For patients with T3/N1 disease, there was a lesser effect, and for patients with T3/N2 disease, no discernible effect was visible. This suggests stage migration. If the effect was based simply on the surgeon performing a better operation, I would expect that the largest effect would be among the patients with N2 disease.

In reality, good surgery and good pathology probably both count, not just one or the other.

DR LOVE: What about the prognosis for patients who have received neoadjuvant radiation therapy and chemotherapy for rectal cancer? How do you interpret nodes?

DR TEPPER: It's harder to interpret the node count for those patients. One still should be able to define nodes in those patients, but the gold standard of a minimum of 13 or 14 nodes probably doesn't apply, and you probably can't have that as a reasonable standard.

A couple of studies have examined this issue and found an increased difficulty in finding nodes in those patients (Wichmann 2002; Beresford 2005; Thorn 2004; Luna-Perez 2003).

CD 1, Track 9

DR LOVE: What new clinical research approaches are currently under way for rectal cancer, including combined chemotherapy/radiation therapy regimens?

DR TEPPER: We've tried to coordinate the adjuvant trials in rectal cancer in the United States through a group previously called the GI Intergroup, which is now known as the GI Steering Committee of the National Cancer Institute's Clinical Trials Working Group.

Two carefully designed trials have recently started that allow patients to enroll in both studies. The first is the NSABP-R-04 study that is evaluating preoperative radiation and chemotherapy for rectal cancer patients.

The study has a two-by-two randomization scheme in which patients are initially assigned either to continuous infusion 5-FU or to capecitabine plus or minus oxaliplatin, with radiation therapy.

The idea was to use oxaliplatin to increase the rate of pathologic complete response, improve the local control rate, and perhaps offer additional beneficial systemic effects (1.1).

After patients complete preoperative therapy and undergo surgery, they can be enrolled in an ECOG study in which patients are randomly assigned to FOLFOX either alone or with bevacizumab.

The entry criteria are basically what they've been for almost all of the rectal studies to date: The patients must have T3 and/or node-positive disease. ■

1.1

Preoperative Radiotherapy (RT) Combined with Capecitabine and Oxaliplatin versus Radiotherapy Combined with 5-FU and Oxaliplatin in Patients with Resectable Rectal Cancer

Protocol ID: NSABP-R-04, NCT00058474
Target accrual: 1,606

Eligibility

- Adenocarcinoma of the rectum
- Surgically resectable disease
- Located <12 cm from the anal verge
- ≥18 years of age

R

- Arm 1: continuous infusion 5-FU 225 mg/m²/day for 5 days/week on days of planned RT*
- Arm 2: same as arm 1, plus oxaliplatin 50 mg/m² weekly x 5 during RT*
- Arm 3: capecitabine 825 mg/m² BID 5 days per week on days of planned RT*
- Arm 4: same as arm 3, with oxaliplatin 50 mg/m² weekly x 5 during RT*

* 4,500 cGy in 25 fractions over five weeks with a 540 cGy boost in three fractions for nonfixed tumors or a 1,080 cGy boost in six fractions for fixed tumors

SOURCE: NSABP-R-04 Protocol, October 27, 2005.

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Glynne-Jones R et al. **Socrates phase II study results: Capecitabine (CAP) combined with oxaliplatin (OX) and preoperative radiation (RT) in patients (pts) with locally advanced rectal cancer (LARC).** *Proc ASCO* 2005;**Abstract 3527**.

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Gunderson LL et al. **Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer: A pooled analysis.** *Int J Radiat Oncol Biol Phys* 2002;54(2):386-96. **Abstract**

Luna-Perez P et al. **Prognostic significance of retrieved lymph nodes per specimen in resected rectal adenocarcinoma after preoperative chemoradiation therapy.** *Arch Med Res* 2003;34(4):281-6. **Abstract**

Tepper JE et al. **Impact of number of nodes retrieved on outcome in patients with rectal cancer.** *J Clin Oncol* 2001;19(1):157-63. **Abstract**

Thorn CC et al. **What factors affect lymph node yield in surgery for rectal cancer?** *Colorectal Dis* 2004;6(5):356-61. **Abstract**

Wichmann MW et al. **Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer.** *Arch Surg* 2002;137(2):206-10. **Abstract**

Willett CG et al. **Surrogate markers for antiangiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: Continued experience of a phase I trial in rectal cancer patients.** *J Clin Oncol* 2005;23(31):8136-9. **Abstract**

INTERVIEW

J Randolph Hecht, MD

Dr Hecht is Clinical Professor of Medicine and Director of the UCLA GI Oncology Program in the Division of Hematology/Oncology in the Department of Medicine at UCLA School of Medicine in Los Angeles, California.

CD 1, Tracks 17-27 – CD 2, Tracks 1-9

CD 1

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- **Track 18** Mechanism of action of small-molecule tyrosine kinase inhibitor PTK/ZK
- **Track 19** Dynamic contrast-enhanced MRI as a surrogate marker for response to PTK/ZK
- **Track 20** Mechanisms of VEGF inhibition
- **Track 21** Differences in the potential roles of VEGF receptors 1, 2 and 3
- **Track 22** Efficacy of single-agent PTK/ZK
- **Track 23** Background and design of the CONFIRM-1 and CONFIRM-2 trials
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CD 2

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- **Track 5** Clinical use of bevacizumab in the adjuvant setting
- **Track 6** Duration of treatment with bevacizumab
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Select Excerpts from the Interview

CD 1, Tracks 23-26

DR LOVE: Can you describe the CONFIRM trials, which studied the use of PTK/ZK (vatalanib) in patients with untreated metastatic colon cancer?

DR HECHT: CONFIRM-1 enrolled previously untreated patients with metastatic colorectal cancer (Hecht 2005), and CONFIRM-2 evaluated

second-line treatment of patients with metastatic colorectal cancer. All patients in the CONFIRM-1 study received 5-fluorouracil and oxaliplatin, administered as FOLFOX-4.

Patients were randomly assigned to receive either 1,250 mg of PTK/ZK daily or placebo. The identical regimen was used in CONFIRM-2 for patients who had failed treatment with 5-fluorouracil and irinotecan.

DR LOVE: Can you discuss the trial results?

DR HECHT: In both CONFIRM trials, progression-free survival was measured rigorously using a central assessment, which was completely blinded as to how the patient was doing clinically.

In CONFIRM-1, the final progression-free survival analysis showed a modest improvement, which was not significant (HR = 0.88), but investigator-assessed progression-free survival, a more common measurement, did reach statistical significance (HR = 0.83; $p = 0.026$).

Progression-free survival was one of two primary endpoints; the other was overall survival. At this time, we only have data for progression-free survival, and that's what was presented at ASCO 2005 (Hecht 2005).

One of the things seen in CONFIRM trials that I think was very interesting was the correlation of progression-free survival and LDH, which has been evaluated as both a prognostic indicator and a predictive marker for chemotherapy. Historically, LDH has been used as a stratification criterion to make certain both arms of a study are balanced. In these trials, LDH and performance status were used as stratification criteria.

When you look at the patients who had high LDH – the worst-prognosis group – they derived the greatest benefit from PTK/ZK. In fact, with the addition of PTK/ZK, the hazard ratio of 0.88 decreased to 0.68 for centrally assessed progression-free survival.

CD 2, Track 1

DR LOVE: I am curious about your thoughts on the antitumor mechanism of action of bevacizumab.

DR HECHT: The original thinking was that bevacizumab inhibited the growth of new blood vessels. In order for tumors to grow beyond a certain size, the angiogenic switch is flipped, and a mutation causes the secretion of growth factors, which leads to the supply of new blood vessels to the tumor.

However, another name for vascular endothelial growth factor is vascular permeability factor. Tumor blood vessels are leaky, and tumors tend to have a high intratumoral pressure. One of the thoughts — this is sometimes called the Jain hypothesis (Jain 2001) — is that the vasculature that's associated with tumors is abnormal. It's tortuous. The vessels are dilated, inefficient, and also very leaky. By giving anti-angiogenic therapy, you might be normalizing the vasculature.

This process would have several effects (2.1), one of which could be to allow a more efficient delivery of chemotherapy by providing more efficient blood vessels and by reducing intratumoral pressure. It's harder to get chemotherapy in against a pressure gradient.

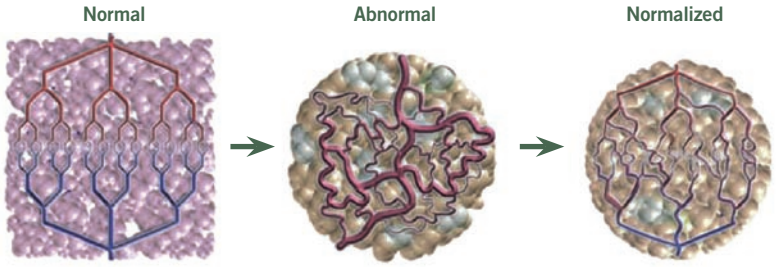
A study by Chris Willett (Willett 2004), published in *Nature Medicine*, had a huge impact in terms of this thinking, although it had a small number of patients. The study showed that following treatment of rectal cancer with bevacizumab, blanching and shrinkage of the tumor occurred and less blood (ie, perfusion and volume) appeared to be going to the tumor (2.2).

In addition, interstitial pressure of the tumor fell and significant decreases in microvascular density occurred. This observation was made using bevacizumab alone, which offers some validation that at least a portion of the Jain hypothesis appears to be correct.

Bevacizumab increases response rates, and no one expected anti-angiogenic therapies to increase response rates. All we ever expected was to cause stabilization of disease by keeping new blood vessels from growing. Instead, virtually all the trials with bevacizumab have shown an increase in response rate.

In fact, the colon cancer trials — the original 5-FU trial that Kabbinavar published (Kabbinavar 2003), the IFL study by Herb Hurwitz (Hurwitz 2004), Kabbinavar's other 5-FU trial (Kabbinavar 2005), the TREE-2 trial (Hochster 2005, 2006) — all show approximately a 10 percent improvement in response rate with the addition of bevacizumab.

2.1 **Effect of Anti-VEGF on Normalization of Tumor Vasculature**



Anti-VEGFR treatment prunes immature blood vessels and decreases the diameter of residual vessels. The tumor vasculature becomes less tortuous and more organized, with improved perivascular cells and basement membrane coverage.

SOURCE: Adapted by permission from Macmillan Publishers Ltd: *Nature Medicine* (Jain RK. **Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy.** *Nat Med* 2001;7(9):987-9), copyright 2001. No abstract available

CD 2, Track 4

DR LOVE: Do you continue using bevacizumab in a patient who has disease progression?

DR HECHT: Nobody knows the best approach in this situation, and there are studies in development right now to answer that question. One of the problems has been that the standard of care in colon cancer has changed so rapidly that it's been difficult to catch up and fill in all the gaps.

The ECOG-E3200 trial, which Bruce Giantonio presented at ASCO this year (Giantonio 2005), showed that the combination of FOLFOX and bevacizumab was better than FOLFOX alone in patients who were bevacizumab-naïve and who had failed an irinotecan-containing regimen. However, that group of patients no longer exists because there are very few patients who don't receive bevacizumab front line.

The answer depends on how bevacizumab works. If bevacizumab works only by blocking the growth of new blood vessels, maybe giving it after disease progression doesn't make any sense.

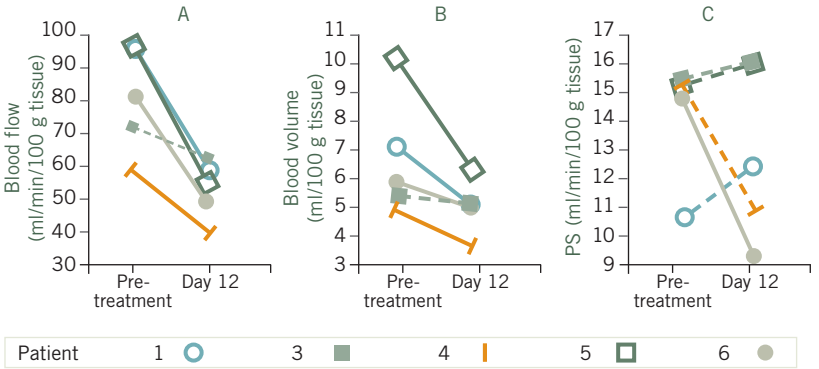
However, if bevacizumab works by facilitating the delivery of chemotherapy, perhaps it does make some sense.

DR LOVE: What do you do in your own practice?

DR HECHT: I have a discussion with the patient. Theoretically, it could make sense to continue treatment; however, more toxicity might occur. We try to enroll the patient in a clinical trial, since we are in an academic medical center, but I do present that option to my patients.

2.2

Effect of Anti-VEGF Therapy on Blood Flow and Volume and Vascular Permeability



"Effect of a single injection of bevacizumab on tumor vasculature and FDG uptake. Parameters were obtained pretreatment and after one bevacizumab infusion. (A–C) blood perfusion (A), blood volume (B) and permeability-surface area product (PS; C). Significant decreases after treatment are indicated by solid lines ($p < 0.05$ by *t*-test). Blood flow and blood volume decreased significantly in four of the patients."

SOURCE: Adapted by permission from Macmillan Publishers Ltd: *Nature Medicine* (Willett CG et al. **Direct evidence that the VEGF-specified antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004;10(2):145-7), copyright 2004. **Abstract**

CD 2, Tracks 6-7

DR LOVE: The AVANT trial, like the NSABP-C-08 trial, is considering what might be the most interesting question in adjuvant therapy right now: the use of bevacizumab. However, it is also comparing capecitabine to infusional 5-FU. What are your thoughts on this?

DR HECHT: I believe that this will provide another therapy option. Personally, I have patients who are very happy with infusional 5-FU, even when given the choice between the two agents.

Other patients may prefer not to have a central line or may not want to wear a pump, but remember that oxaliplatin requires a central line anyway.

The issue that will remain unanswered following those trials is the optimal duration of bevacizumab. One thought was that if you were preventing the growth of new blood vessels, maybe bevacizumab should be given to patients for the rest of their lives.

Obviously, that's not a practical option from either a toxicity standpoint or a resource standpoint.

How long do you treat? Remember, we still don't know how long to treat with cytotoxic agents. Some data — British data, for example — suggest shorter courses of chemotherapy may be as good as six-month regimens.

Not long ago, we were treating patients for a year. At this time, we're continuing the fluoropyrimidine/oxaliplatin and bevacizumab for six months.

DR LOVE: Do you use capecitabine with oxaliplatin in the clinical adjuvant setting?

DR HECHT: I have done so in special circumstances. The data from an efficacy standpoint showing functional equivalence between capecitabine-containing regimens and infusional fluorouracil-containing regimens are good (Twelves 2005a, b).

Randomized Phase III trials of capecitabine alone versus 5-fluorouracil have been conducted (Twelves 2005a, b), so the use of capecitabine in this setting is not a huge extrapolation. ■

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INTERVIEW

Josep Tabernero, MD

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Track 12 Arteriovascular exclusionary criteria in the AVANT trial

Track 13 Adjuvant chemotherapy for patients with Stage II and III disease

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Track 15 Capecitabine dosing in the adjuvant setting

Track 16 Proposed trials of cetuximab in the adjuvant setting

Track 17 Incorporating bevacizumab/cetuximab therapies into clinical practice

Track 18 Clinical trial results of irinotecan-containing regimens in the adjuvant setting

Track 19 NSABP-C-07: Comparison of toxicity with FLOX versus FOLFOX

Track 20 Role of calcium and magnesium for oxaliplatin-related neurotoxicity in the adjuvant and metastatic settings

Track 21 Management of oxaliplatin-related neuropathy

Track 22 Safety and efficacy of neoadjuvant oxaliplatin for rectal cancer

Track 23 Future directions in the management of colorectal cancer

Select Excerpts from the Interview

CD 2, Track 11

DR LOVE: What was the rationale for looking at CAPOX in the AVANT trial?

DR TABERNERO: Results from a large Phase II study in metastatic disease showed that CAPOX (oxaliplatin/capecitabine) has at least the same efficacy as FOLFOX-4 (Tabernero 2002), so the next step was to further test this combination in both the metastatic and adjuvant settings.

In the metastatic setting, preliminary results of Phase III studies show that CAPOX has the same efficacy in terms of response rate and time to progression and a better safety profile than oxaliplatin and 5-fluorouracil-based combinations (Sastre 2005; Arkenau 2005).

So we want to move this chemotherapy schedule to the adjuvant setting. In addition to safety, another important issue with this schedule is patient convenience. With CAPOX patients come to the hospital or medical facility once every three weeks, and they take pills for two weeks at home.

DR LOVE: What do we know about the combination of CAPOX and bevacizumab?

DR TABERNERO: We have the results of two different studies. The first study was the TREE-2 study (Hochster 2005a, 2006), which was a randomized Phase II study with three different arms. One of the arms studied a combination of CAPOX and bevacizumab. Data from this arm were compared with those from an arm of the TREE-1 study that studied CAPOX alone.

These data showed a clear increase in response rate with a similar safety profile compared to CAPOX alone (Hochster 2005b).

The other experience we have right now is that presented by Dr Fernando this year at the ASCO meeting (Fernando 2005). It was interesting to see that the median time to progression was almost 12 months using a different schedule of CAPOX and bevacizumab. That is very relevant.

DR LOVE: Do you think the combination of CAPOX and bevacizumab is a rational first-line clinical alternative for metastatic disease?

DR TABERNERO: I would say yes. From a regulatory point of view, you definitely need the data from Phase III studies, but at this time, especially in the United States, some physicians are treating patients with the combination of CAPOX and bevacizumab.

The safety reports from patients who are treated with this regimen do not cause us to anticipate any different safety issues than those associated with FOLFOX-4.

CD 2, Track 12

DR LOVE: What are the exclusion criteria for the AVANT trial in terms of prior cardiovascular disease?

DR TABERNERO: They rule out patients with what we call active ischemic arterial disease — not only cardiac disease, but also other arterial diseases (3.1). This means that patients who've had an arterial event must be without signs and symptoms for one year with disease control.

The same goes for arterial hypertension. Arterial hypertension must be well controlled with either diet or medical treatment.

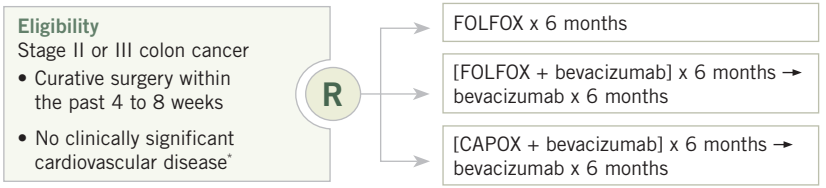
But this is only one requirement for treating patients in the AVANT study. The other thing we stress to the patients is that they need close follow-up. I request at least three blood pressure readings per week for the first treatment cycle.

If I see that the patient has no problem with hypertension, I reduce the follow-up requirement. But at the beginning of treatment, I think this is important.

3.1

AVANT Adjuvant Study: Phase III Randomized Trial Comparing FOLFOX to FOLFOX Plus Bevacizumab and CAPOX Plus Bevacizumab in Patients with Resected Colon Cancer

Target accrual: 3,450 (Temporarily closed)
Protocol IDs: UCLA-0412086-01, ROCHE-BO17920A, NCT00112918



* Cerebrovascular accident within past 6 months; myocardial infarction within the past year; uncontrolled hypertension while on chronic medication; unstable angina; NYHA Class II-IV heart failure; serious cardiac arrhythmias that require medication

SOURCE: NCI Physician Data Query, March 2006.

CD 2, Track 13

DR LOVE: Can you talk about your decision-making approach off protocol in terms of adjuvant therapy for Stage III and Stage II disease?

DR TABERNERO: I'm convinced of the effects of oxaliplatin-based chemotherapy, especially FOLFOX-4, in the adjuvant setting.

I discuss the risks of disease recurrence with patients with a 5-fluorouracil/leucovorin-based chemotherapy or FOLFOX. Very few patients are opposed to treatment with oxaliplatin-based chemotherapy, so my standard has been to begin patients with FOLFOX-4 for 12 cycles.

DR LOVE: How do you approach Stage II disease?

DR TABERNERO: I give the same recommendations; although the recurrence risk is lower for some patients with Stage II disease, for others it's even higher than that for Stage III disease. I believe the relative reduction in the recurrence risk is almost the same with chemotherapy.

Chemotherapy does not discriminate the tumor stage, and chemotherapy reduces the risk of relapse. You need to determine not only the absolute figures but also the relative figures.

Patients who are in very good condition, in a very healthy state, without any disease that might compromise their life in the next five to seven years usually want to have as much treatment as possible to decrease the risk of recurrence.

So my recommendation is to give FOLFOX-4 to patients with high-risk Stage II disease.

CD 2, Track 14

DR LOVE: Could you summarize your take on the X-ACT trial?

DR TABERNERO: When the X-ACT trial (Twelves 2005) results were presented, they impressed us because we had expected equivalence between capecitabine and 5-fluorouracil/leucovorin. Instead, we were shown some impressive advantages in relapse-free survival and disease-free survival (3.2).

I think the good news is that capecitabine is an alternative for patients who are reluctant to receive oxaliplatin because they fear polyneuropathy or they may even fear receiving intravenous chemotherapy.

The only bad news from the X-ACT study was that patients with high-risk Stage II disease were not included in the trial.

So, unfortunately, the regulatory approval of capecitabine will include only patients with Stage III disease. In some countries, it might be difficult at times to use capecitabine in the adjuvant treatment of patients with high-risk Stage II disease.

3.2

Efficacy of the Major Endpoints of the X-ACT Trial over a Median Follow-Up Period of 3.8 Years

Endpoint	Hazard ratio (95% CI)	*p*-value for equivalence	*p*-value for superiority
Disease-free survival			
Capecitabine	0.87 (0.75-1.00)	<0.001	0.05
Fluorouracil plus leucovorin			
Relapse-free survival			
Capecitabine	0.86 (0.74-0.99)	—	0.04
Fluorouracil plus leucovorin			
Overall survival			
Capecitabine	0.84 (0.69-1.01)	<0.001	0.07
Fluorouracil plus leucovorin			

SOURCE: Twelves C et al. *N Engl J Med* 2005;352(26):2696-704. **Abstract**

CD 2, Track 22

DR LOVE: In a clinical setting, how do you decide between capecitabine and infusional 5-FU for neoadjuvant therapy of rectal cancer?

DR TABERNERO: I give the option to the patient. I'm used to administering 5-fluorouracil as a continuous infusion, and I feel comfortable using it. But a number of patients complain about having a pump continuously for six or

seven weeks, so this is an issue. If patients have concerns about the pump, I give them the opportunity to receive capecitabine as an alternative. ■

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following is true regarding staging for rectal cancer?**
   a. N stage and T stage are both important and independent predictors of outcomes
   b. The number of nodes found has a large impact on outcomes
   c. Nodes are harder to identify after radiation and/or chemotherapy
   d. All of the above

2. **During the CONFIRM-1 trial for patients with previously untreated metastatic colorectal cancer, those who received FOLFOX-4 with PTK/ZK experienced significant improvement in centrally assessed progression-free survival compared to patients who received FOLFOX-4 alone.**
   a. True
   b. False

3. **According to the Jain hypothesis, anti-VEGF treatment may work by normalizing tumor vasculature, which is often dilated, inefficient and leaky.**
   a. True
   b. False

4. **In a small study of patients with rectal cancer, bevacizumab was associated with changes in tumor physiology that included decreased _____.**
   a. Tumor blood perfusion
   b. Tumor blood volume
   c. Intratumoral pressure
   d. Microvascular density
   e. All of the above

5. **For patients with metastatic disease, preliminary results from Phase III studies show CAPOX is not comparable to oxaliplatin- and fluorouracil-based combinations.**
   a. True
   b. False

6. **The X-ACT trial demonstrated that patients who received capecitabine experienced advantages in _____ compared to those who received 5-fluorouracil/leucovorin for adjuvant treatment of Stage III disease.**
   a. Disease-free survival
   b. Relapse-free survival
   c. Overall survival
   d. Disease-free and relapse-free survival
   e. All of the above

7. **The NSABP-R-04 trial will evaluate the efficacy of capecitabine or 5-fluorouracil with and without oxaliplatin as neo-adjuvant treatment of resectable rectal cancer.**
   a. True
   b. False

8. **In the CONFIRM trials, patients with high LDH levels derived a greater benefit from PTK/ZK than patients who did not have high LDH levels.**
   a. True
   b. False

9. **A staging analysis of patients from the Gastrointestinal Intergroup Study 0411 determined that in patients with T3/N0 disease, the outcome was worse if the pathologist found:**
   a. Zero to eight nodes
   b. Eight to 13 nodes
   c. 14 or more nodes

10. **Exclusionary criteria for the AVANT trial include:**
    a. Myocardial infarction within the past year
    b. Unstable angina
    c. NYHA Class II-IV heart failure
    d. All of the above
    e. None of the above

Post-test answer key: 1d, 2b, 3a, 4e, 5b, 6d, 7a, 8a, 9a, 10d

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- Counsel appropriate patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging research data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients. . . . . 5 4 3 2 1 N/A
- Evaluate emerging research data on various neoadjuvant radiation therapy/chemotherapy approaches to rectal cancer and explain the absolute risks and benefits of these regimens to patients. . . . . 5 4 3 2 1 N/A
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
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J Randolph Hecht, MD	5 4 3 2 1	5 4 3 2 1
Josep Tabernero, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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Will help me improve patient care. . . . . 5 4 3 2 1 N/A
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Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
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Colorectal Cancer™

U P D A T E

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