5 Minute JournalClub

Key ASCO Presentations
Issue 8, 2010

Use of Bevacizumab in the Maintenance Setting for Patients with Metastatic Colorectal Cancer (mCRC)

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Compare and contrast the efficacy and safety of single-agent bevacizumab and continued XELOX/bevacizumab as maintenance treatment for mCRC.

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No real or apparent conflicts of interest to disclose.

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Advisory Committee: Bristol-Myers Squibb Company, ImClone Systems Incorporated; Paid Research: Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals Inc.

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To go directly to the slides and commentary, **click here**.

Medical oncology has always challenged both patient and physician to make brutally difficult decisions concerning treatments that often provide modest benefits at the expense of significant toxicity. Nowhere has this paradigm been more evident than at the recent GI session in Chicago where French investigators **reported** that in advanced pancreatic cancer FOLFIRINOX (with full-dose oxaliplatin and irinotecan) not only improved progression-free survival and response rate but also overall survival (from 6.8 to 11.1 months). Within a couple of weeks of the presentation, I had chatted with Rich Goldberg, Axel Grothey and Malcolm Moore about this controversial data set. The bottom line? In spite of increased myelosuppression, particularly neutropenia, and other predictable problems with the combination, all three investigators are now considering FOLFIRINOX for younger, healthier patients.

Another provocative **data set** out of ASCO was a Spanish trial demonstrating that in patients receiving XELOX/bevacizumab as first-line therapy for metastatic colon cancer, maintenance therapy with bev alone may be as effective as maintenance with XELOX/bev. Axel, who was still a bit cranky after watching Spain run circles around his German team in the World Cup, believes this study has an inferior design to the ongoing German trial comparing capecitabine/bev to bev as maintenance that also includes a control arm of no maintenance.

The latest in a series of innovative pilot studies from Memorial examining local therapy in colon and rectal cancer also generated some buzz in Chicago. Deborah Schrag **reported** on 30 patients with T2-3 primary rectal cancer, many with nodal mets, who received pre-op FOLFOX/bev *without* radiation therapy. The resectability rate in this experience was similar to those that have been seen with neoadjuvant chemo/radiation therapy. Although this strategy is far from ready for prime time, Axel told me about a patient he had recently treated with this approach because prior radiation therapy for cervical cancer precluded further RT. Perhaps not surprisingly, she responded to FOLFOX and then underwent successful surgery.

Several other notable ASCO papers focused on EGFR antibody treatment for colorectal cancer, specifically cetuximab. K-ras status (wild type) was once again determined to have predictive value in the metastatic setting while B-raf was not, and data from an **NCCTG trial** evaluating mFOLFOX6 alone or with cetuximab in the adjuvant setting

disappointingly demonstrated no additional benefit with the combination, regardless of K-ras status.

The concluding sound bite from this, our final ASCO highlights issue, is another chemo/bev study that resulted in a response and a progression-free survival advantage but no survival benefit. "**AVAGAST**" focused on gastric cancer, and because survival was the primary endpoint, the study was considered negative. At the prostate cancer session, similar results and conclusions were reported for docetaxel/bevacizumab, and the recent ODAC opinion on chemo/bev in breast cancer suggests that the acceptability bar is being raised, even for an agent whose most significant toxicity is often financial.

Enjoy the rest of your summer. We will be back right around Labor Day with our next installment of Consensus or Controversy — this time in non-small cell lung cancer.

Neil Love, MD
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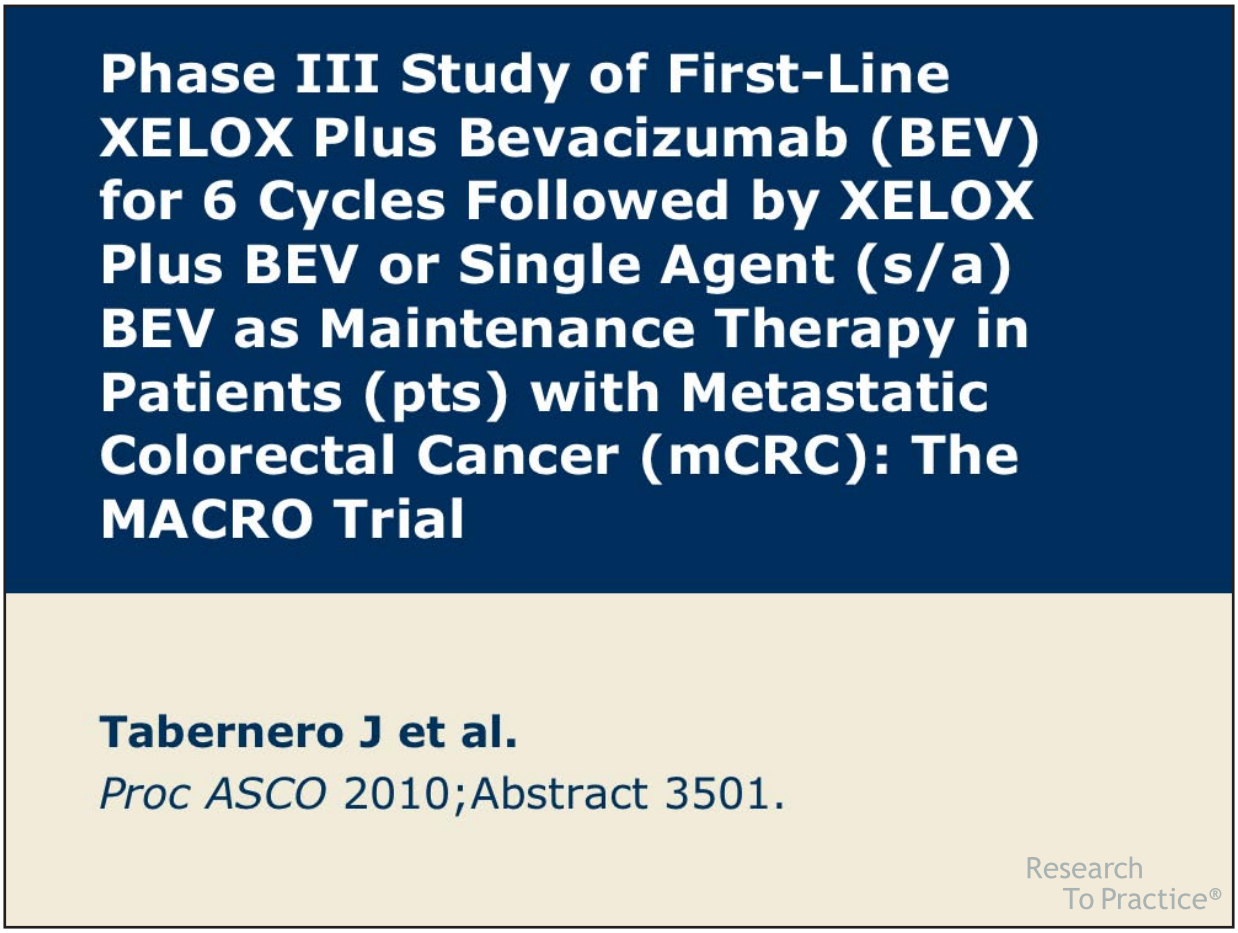
Use of Bevacizumab in the Maintenance Setting for Patients with Metastatic Colorectal Cancer (mCRC)

Presentation discussed in this issue

Tabernero J et al. **Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single-agent BEV as maintenance therapy in patients with metastatic colorectal cancer: The MACRO trial.** *Proc ASCO* 2010;**Abstract 3501**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Richard M Goldberg, MD (6/23/10), Axel Grothey, MD (7/9/10) and Alan P Venook, MD (6/16/10)



Background

- Optimal duration of first-line treatment of metastatic colorectal cancer (mCRC) is still under debate.
  - Some physicians continue the initial treatment until an unacceptable toxicity or progression occurs.
  - Others may stop all or part of the treatment after the initial four to six months of therapy.
- Bevacizumab (Bev) has a good long-term safety profile and studies suggest that the maximum benefit may be observed when it is maintained until disease progression.
- **Current study objective:**
  - To demonstrate the safety and efficacy of s/a Bev maintenance after six cycles of induction chemotherapy with XELOX + Bev compared to continued XELOX + Bev.

Tabernero J et al. *Proc ASCO* 2010;Abstract 3501.

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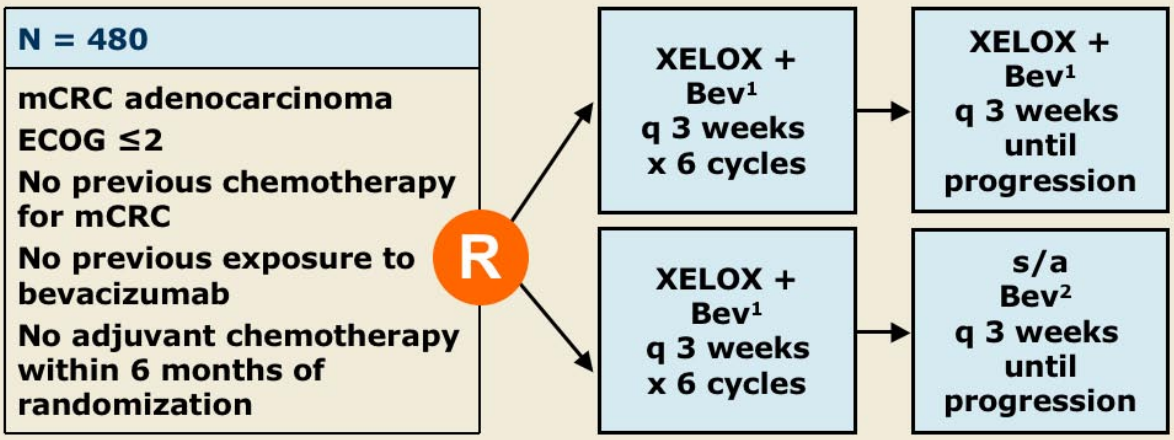
Study Design: MACRO Trial



[1] XELOX + Bev: oxaliplatin 130 mg/m^2 IV d1, capecitabine 1,000 mg/m^2 PO BID d1-14, Bev 7.5 mg/kg IV d1

[2] s/a Bev 7.5 mg/kg IV d1

Tabernero J et al. *Proc ASCO* 2010;Abstract 3501.

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Statistical Design

- Non-inferiority design:
  - 10-month median progression-free survival (PFS) on control arm
  - Non-inferiority limit of 7.6 months and hazard ratio (HR) = 1.32
  - Alpha error = 0.025, one sided
  - Power = 80%

Tabernero J et al. *Proc ASCO* 2010;Abstract 3501.

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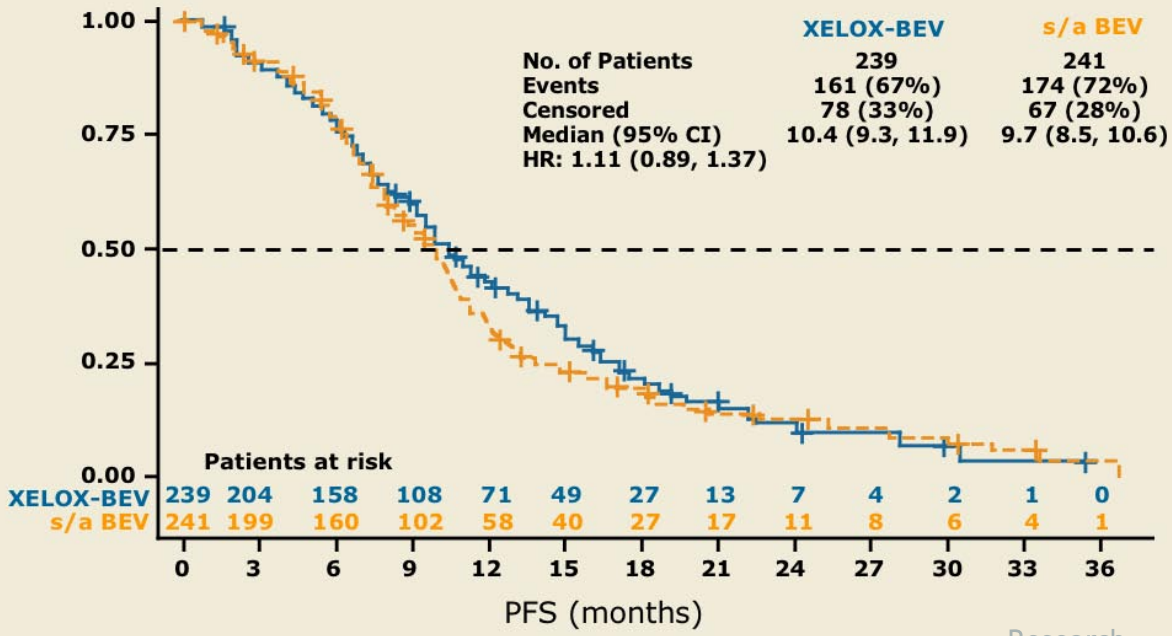
Median Progression-Free Survival



With permission from Tabernero J et al. *Proc ASCO* 2010;Abstract 3501.

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Efficacy Endpoints

	Continued XELOX + Bev (n = 239)	s/a Bev Maintenance (n = 241)	HR (95% CI)
Median progression-free survival	10.4 mo	9.7 mo	1.11 (0.89, 1.37)
Median overall survival	23.4 mo	21.7 mo	1.04 (0.81, 1.32)
Confirmed overall response rate	46%	49%	0.89* (0.62, 1.27)

* Value shown represents the odds ratio for the confirmed overall response rate.

Tabernero J et al. *Proc ASCO* 2010;Abstract 3501.

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Select Grade 3/4 Treatment-Related Adverse Events

Adverse Event	Continued XELOX + Bev (n = 238)	s/a Bev Maintenance (n = 238)
Paresthesia	24.8%	7.6%
Diarrhea	10.9%	13.9%
Hand-foot syndrome	12.2%	6.7%
Hypertension	3.8%	7.1%
Thrombosis	0.8%	1.3%
GI perforation	0.8%	0.4%
Bleeding	0.4%	0.4%

Tabernero J et al. *Proc ASCO* 2010;Abstract 3501.

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Conclusions

- Since the 95% CI of the hazard ratio crossed the a priori limit of 1.32, the a priori specified non-inferiority limit of 7.6 months for PFS cannot be confirmed.
- This study suggests that maintenance therapy with single-agent bevacizumab may be an appropriate treatment option following induction XELOX-bevacizumab in patients with mCRC.
- Other studies evaluating the maintenance treatment with Bev after standard chemotherapy in mCRC are under recruitment and evaluation (DREAM, CAIRO-3, AIO-ML21768).

Tabernero J et al. *Proc ASCO* 2010;Abstract 3501; Venook AP. *Proc ASCO* 2010; Discussant.

Investigator comment on the results of MACRO

MACRO utilized a noninferiority design, powered to prove that stopping chemotherapy and continuing bevacizumab was as good as continuing chemotherapy with bevacizumab. The bottom line was that there was not proof of noninferiority. The differences in outcome, however, were minor, with only about a two-month difference in median overall survival in favor of continuing chemotherapy. The other finding was that a 1,000 mg/m^2 dose of capecitabine proved to be too toxic for a lot of patients, and I wouldn't necessarily use this regimen without dose reducing the capecitabine in clinical practice.

I don't think that anybody has a right to be dogmatic about the clinical implications of these results. I tend to evaluate every patient individually. I manage patients with minimal disease quite differently than I do those with bulky disease, for which my preference is to continue them on continuous chemotherapy and a biologic agent. This particularly applies to patients who have peritoneal disease because I'm always worried that their first progression will be catastrophic. In patients with minimal disease, it's perfectly reasonable to either take a break from chemotherapy, as long as you watch the patients carefully, or to keep the patients on bevacizumab.

Interview with Richard M Goldberg, MD, June 23, 2010

Investigator comment on the results of MACRO

MACRO used a noninferiority design, and the investigators were generous with their margins of error. I'm not quite happy that they allowed a detrimental effect of 32 percent, or a hazard ratio of 1.32, to still be considered noninferior. There were also other design flaws, which hamper our ability to interpret these data. There wasn't a control arm, in that bevacizumab was included in both arms, and CAPOX was continued beyond six cycles, which resulted in 25 percent of the patients having Grade III/IV neurotoxicity, which I think is unacceptable.

The hazard ratio was 1.11, meaning that there was an 11 percent detrimental effect. However, the 95-percent confidence interval included 1.37, meaning a 37 percent detrimental effect. So this was a negative trial and bevacizumab monotherapy cannot be considered a standard approach.

My default for patients when I initiate an oxaliplatin-based regimen, have a clear palliative scenario and am not considering liver metastasectomy is to discontinue oxaliplatin after eight cycles of FOLFOX or six cycles of CAPOX and continue the fluoropyrimidine and bevacizumab as maintenance therapy. This is my treatment-to-progression approach, which I use as a default for most of my patients.

Interview with Axel Grothey, MD, July 9, 2010

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Investigator comment on the results of MACRO

This study attempted to evaluate the issue of maintenance bevacizumab. The authors stated that they set out to make this a noninferiority trial, so they could prove that continuing bevacizumab alone was equivalent to continuing chemotherapy and bevacizumab, but the study was underpowered. Having said that, patients did about the same in both arms, more or less.

In broad strokes, the data suggest that you can do without continuing the chemotherapy, and bevacizumab alone may keep the disease steady. However, there was no treatment control arm. We don't know if bevacizumab was necessary. Additionally, there was a lot of toxicity with continuing XELOX. The patients had approximately the same length of life but a poorer quality of life.

I don't believe this study affects clinical practice much, but it is a reminder that even in the original studies with bevacizumab, there was modest activity and it's not out of the question that bevacizumab could be used by itself in selected patients. However, this study does not establish that approach. In practice, I tend to use a maintenance strategy with 5-FU and bevacizumab, but this is a moving target.

Interview with Alan P Venook, MD, June 16, 2010

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