5 Minute JournalClub

Key ASCO Presentations
Issue 8, 2010

Efficacy and Safety of Bevacizumab with Capecitabine and Cisplatin in Patients with Advanced Gastric Cancer

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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

- Demonstrate knowledge of the efficacy and safety of chemotherapy combined with bevacizumab in the treatment of advanced gastric cancer.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Consulting Agreements: Abraxis BioScience, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Sanofi-Aventis; Paid Research: ACT Biotech Inc, Bristol-Myers Squibb Company, Genta Inc, ImClone Systems Incorporated, Sanofi-Aventis, Taiho Pharmaceutical Co Ltd.

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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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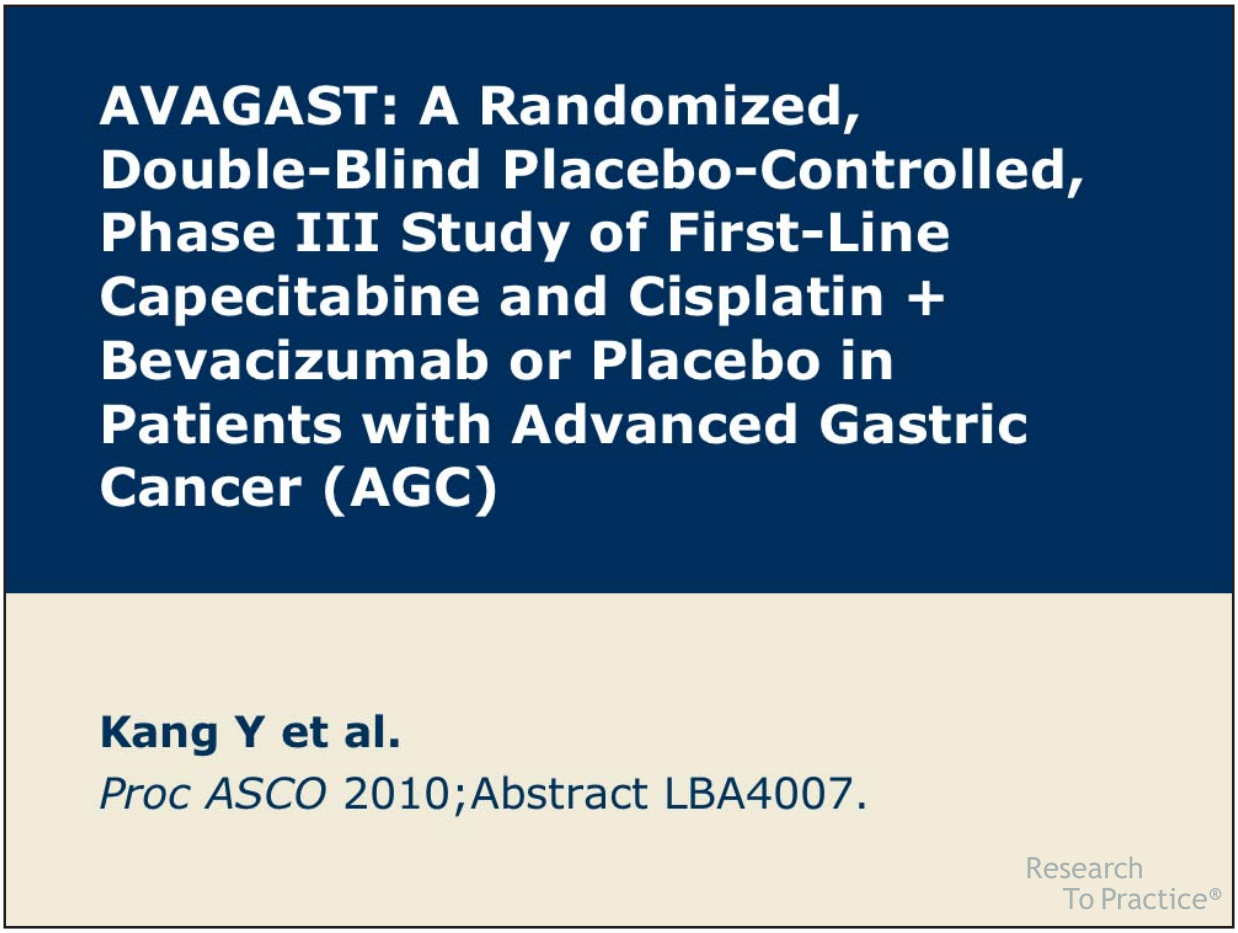
Efficacy and Safety of Bevacizumab with Capecitabine and Cisplatin in Patients with Advanced Gastric Cancer

Presentation discussed in this issue

Kang Y et al. **AVAGAST: A randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer (AGC).** *Proc ASCO* 2010;**Abstract LBA4007**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Jaffer A Ajani, MD (7/9/10) and Richard M Goldberg, MD (6/23/10)



Introduction

- Phase II and III trials have demonstrated improvements in efficacy parameters with the addition of bevacizumab (bev) to chemotherapy for patients with colorectal[1], lung[2] and breast cancers[3] ([1]*NEJM* 2004;350:2335, [2]*JCO* 2005;23:2s, [3]*Breast Can Treat Res* 2005;35:51).
- Bev revealed promising results in Phase II studies for patients with gastric and gastroesophageal junction (GEJ) adenocarcinoma (*JCO* 2005;23:2574).
- **Current study objective:**
  - To investigate the safety and efficacy of bev plus chemotherapy compared to placebo plus chemotherapy in patients with advanced gastric and GEJ adenocarcinoma.
  - Patients were accrued from 93 centers in 17 countries.

Kang Y et al. *Proc ASCO* 2010;Abstract LBA4007.

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AVAGAST Trial Schema

Accrual: 774 (Closed)

Eligibility

Locally advanced/metastatic gastric or GEJ adenocarcinoma
ECOG PS 0-2
No prior chemotherapy

Stratification

Geographic region
Fluoropyrimidine treatment
Disease status

R

XP + Bev (n = 387)
Capecitabine*/Cisplatin (XP) + bev q 3 wks

XP + Placebo (n = 387)
Capecitabine*/Cisplatin (XP) + placebo q 3 wks

*5-FU also allowed if capecitabine was contraindicated.

Capecitabine 1,000 mg/m^2 po bid, d1-14, 1 wk rest; Cisplatin 80 mg/m^2 d1 up to 6 cycles; Bev 7.5 mg/kg d1

Kang Y et al. *Proc ASCO* 2010;Abstract LBA4007.

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AVAGAST Efficacy Data

Survival by Region	XP + Placebo (n = 387)	XP + Bev (n = 387)	Hazard Ratio	*p*-value
Median overall survival (OS)	10.1 mos	12.1 mos	0.87	0.1002
Asia	12.1 mos	13.9 mos	0.97	—
Europe	8.6 mos	11.1 mos	0.85	—
America	6.8 mos	11.5 mos	0.63	—
Median progression-free survival (PFS)	5.3 mos	6.7 mos	0.80	0.0037
Asia	5.6 mos	6.7 mos	0.92	—
Europe	4.4 mos	6.9 mos	0.71	—
America	4.4 mos	5.9 mos	0.65	—

Regional differences in efficacy were observed:

- Longest OS and PFS in both arms were in Asia
- Smallest delta (amount of benefit from bev) was in Asia

Kang Y et al. *Proc ASCO* 2010;Abstract LBA4007.

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Select Grade 3/4 Adverse Events

Adverse Event (AE)	XP + Placebo (n = 381)		XP + Bev (n = 386)	
	Grade 3	Grade 4	Grade 3	Grade 4
Venous thromboembolism (VTE)[1]	6%	3%	4%	3%
Arterial thromboembolism	1%	1%	<1%	<1%
Bleeding[2]	3%	<1%	3%	<1%
Hypertension	<1%	0	6%	0
GI perforations[3]	0	0	2%	0

[1] Grade 5 (XP + placebo arm) <1%. [2,3] Grade 5 (in each study arm) <1%.

Kang Y et al. *Proc ASCO* 2010;Abstract LBA4007.

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Conclusions

- Primary endpoint of OS was not met.
- Secondary efficacy endpoints significantly improved, indicating clinical activity of bev plus chemotherapy in patients with AGC.
  - PFS: 6.7 months vs 5.3 months
  - ORR: 46% vs 37%
- Heterogeneous efficacy results in both treatment arms across geographic regions.
- No unexpected or new safety signals for bev.
- Further analysis is ongoing, including pre-planned biomarker analysis.

Kang Y et al. *Proc ASCO* 2010;Abstract LBA4007.

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Investigator comment on the results of AVAGAST: A Phase III study of first-line capecitabine, cisplatin and bevacizumab for advanced gastric cancer

AVAGAST was a negative trial, but if we examine the data by region, they are quite interesting. If the entire trial had been conducted in Europe and Pan America, it would have been a positive trial. The median overall survival for patients who received capecitabine/cisplatin and bevacizumab was 12.1 months versus 10.1 months in the control arm, but the *p*-value was 0.1.

Investigators collected a lot of blood and tissue in this trial, so they will attempt to determine if they can identify a subset that particularly benefited from the bevacizumab. They are also considering performing a second trial, based on the subgroup analysis, to focus on certain populations for which bevacizumab might be beneficial.

Interview with Jaffer A Ajani, MD, July 9, 2010

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Investigator comment on the results of AVAGAST: A Phase III study of first-line capecitabine, cisplatin and bevacizumab for advanced gastric cancer

AVAGAST is the first study I am aware of evaluating bevacizumab in gastric cancer. The study was conducted mainly in Asia and Europe, and they performed subset analyses because there were different outcomes, dependent upon the region of the world where patients came from.

The addition of bevacizumab resulted in a two-month improvement in overall survival, with a nonsignificant *p*-value of 0.1, and there was a 1.4-month improvement in progression-free survival — 6.7 versus 5.3 months. There was not a lot of toxicity observed, and bleeding and other problems were not observed with bevacizumab.

I don't know that the "book is closed" for bevacizumab in gastric cancer, but it seems unlikely that most physicians would "hop onto the bevacizumab wagon" for gastric cancer on the basis of these data.

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

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