5 Minute JournalClub

Key ASCO Presentations

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CME Information

LEARNING OBJECTIVES

- Employ an understanding of the Phase III efficacy and safety of FOLFIRINOX to identify patients with metastatic pancreatic cancer who may benefit from intensive systemic treatment.
- Compare and contrast the efficacy and safety of single-agent bevacizumab and continued XELOX/bevacizumab as maintenance treatment for mCRC.
- Describe the results of a feasibility study examining neoadjuvant FOLFOX with bevacizumab and without pelvic radiation therapy for patients with locally advanced rectal cancer.
- Counsel patients with metastatic colorectal cancer about the impact of K-ras and B-raf mutation status on disease prognosis and the potential activity of cetuximab.
- Describe the efficacy and safety of cetuximab when added to FOLFOX for patients with Stage III colon cancer who have wild-type or mutant K-ras status.
- Demonstrate knowledge of the efficacy and safety of chemotherapy combined with bevacizumab in the treatment of advanced gastric cancer.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
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 Inc, a wholly owned subsidiary of Celgene Corporation, 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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CME Information (Continued)

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Randomized Phase III Trial Comparing FOLFIRINOX (F: 5FU/Leucovorin [LV], Irinotecan [I], and Oxaliplatin [O]) versus Gemcitabine (G) as First-Line Treatment for Metastatic Pancreatic Adenocarcinoma (MPA): Preplanned Interim Analysis Results of the PRODIGE 4/ACCORD 11 Trial

Conroy T et al.

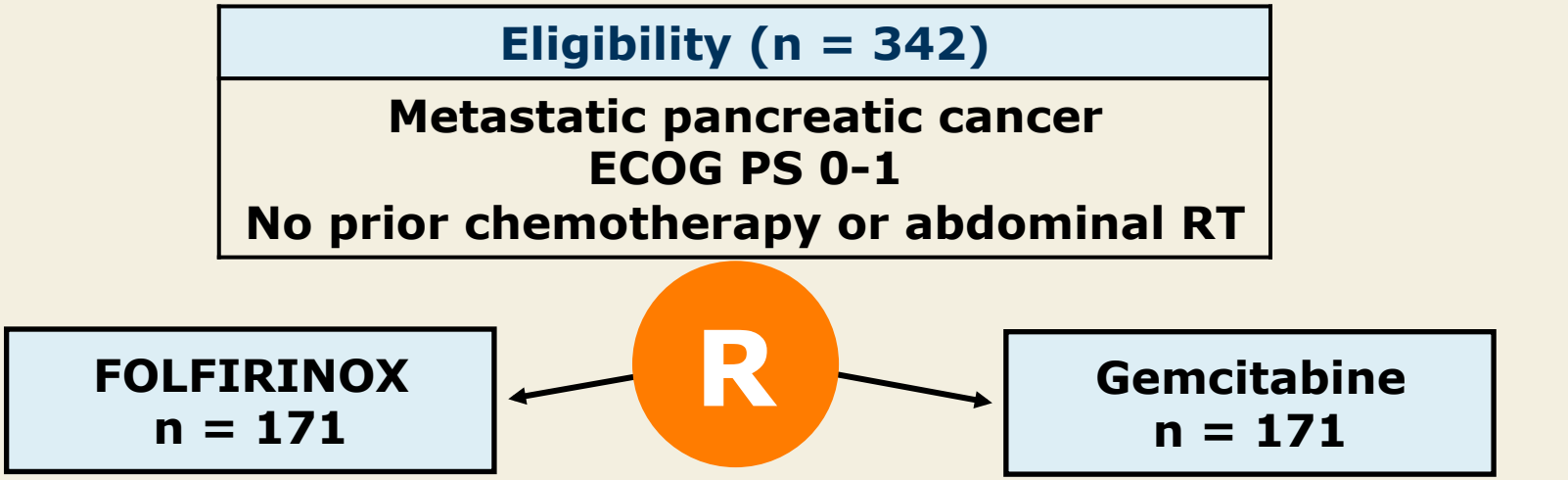
Proc ASCO 2010;Abstract 4010.

Introduction

- Metastatic pancreatic cancer (mPC) is an incurable disease with few good treatment options.
- Single-agent gemcitabine (Gem) is standard treatment with median survival rates of approximately 6-7 months.
- FOLFIRINOX is a promising regimen in patients with advanced PC and a good performance status (PS):
  - Median survival = 10.2 months (*J Clin Oncol* 2005;23:1228)
- Phase II ACCORD 11 study compared FOLFIRINOX to Gem in patients with mPC:
  - Response rate = 31.8% vs 11.4% (*Proc ASCO* 2007;Abstract 4516)
- **Current study objective:**
  - Compare the efficacy and safety of FOLFIRINOX versus Gem in patients with mPC.

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

Phase III PRODIGE 4/ACCORD 11 Study Design



6 months of chemotherapy recommended and CT scans performed every 2 months for both arms

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

Survival

	FOLFIRINOX n = 171	Gem n = 171	Hazard ratio	*p*-value
Median PFS	6.4 months	3.3 months	0.47	<0.0001
Median OS	11.1 months	6.8 months	0.57	<0.0001
1-year survival rate	48.4%	20.6%	—	—
18-month survival rate	18.6%	6%	—	—

PFS = progression-free survival; OS = overall survival

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

Objective Response Rate

	FOLFIRINOX n = 171	Gem n = 171	*p*-value
Complete response (CR)	0.6%	0%	—
Partial response (PR)	31%	9.4%	0.0001
Stable disease (SD)	38.6%	41.5%	—
Disease control (CR + PR + SD)	70.2%	50.9%	0.0003
Progression	15.2%	34.5%	—
Not assessed	14.6%	14.6%	—
Median duration of response	5.9 months	4 months	NS

NS, not significant

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

Grade 3/4 Adverse Events: Hematologic

Adverse Event	FOLFIRINOX n = 167	Gem n = 169	*p*-value
Neutropenia	45.7%	18.7%	0.0001
Febrile neutropenia	5.4%	0.6%	0.009
Anemia	7.8%	5.4%	NS
Thrombocytopenia	9.1%	2.4%	0.008

42.5% of patients in the FOLFIRINOX arm received G-CSF versus 5.3% in the gemcitabine arm.
One toxic death occurred in each arm.

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

Select Grade 3/4 Adverse Events: Non-Hematologic

	FOLFIRINOX n = 167	Gem n = 169	*p*-value
Infection w/o neutropenia	1.2%	1.8%	NS
Peripheral neuropathy	9%	0%	0.0001
Vomiting	14.5%	4.7%	0.002
Fatigue	23.2%	14.2%	0.036
Diarrhea	12.7%	1.2%	0.0001
Alopecia (Grade 2)	11.4%	0.6%	0.0001
Alanine aminotransferase elevation	7.3%	18.6%	0.0022

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

Conclusions

- FOLFIRINOX improves OS and PFS in comparison to Gem for patients with mPC and good PS.
  - Median PFS: 6.4 vs 3.3 months (HR 0.47, $p < 0.0001$)
    - Risk of disease progression reduced by 53%
  - Median OS: 11.1 vs 6.8 months (HR 0.57, $p < 0.0001$)
- FOLFIRINOX is more toxic but has a manageable toxicity profile.
  - Grade 3/4 febrile neutropenia: 5.4% vs 0.6% ($p = 0.009$)
- FOLFIRINOX may be a potential new standard of care for patients with mPC and good PS.
- Plans to evaluate FOLFIRINOX in the adjuvant setting are underway.

Conroy T et al. *Proc ASCO* 2010;Abstract 4010; Tempero M. ASCO 2010. Discussant.

Investigator comment on the results of PRODIGE 4/ACCORD 11: FOLFIRINOX versus gemcitabine as first-line treatment of metastatic pancreatic cancer

This was arguably the most surprising study to be presented in the GI noncolorectal session. The study compared FOLFIRINOX, which is an intensive treatment that uses the full doses of 85 mg/m^2 of oxaliplatin and 180 mg/m^2 of irinotecan and standard doses of 5-FU, to gemcitabine.

The toxicity was obviously greater with the three-drug regimen, and the most noticeable issue was a five percent febrile neutropenia rate compared to a 0.6 percent rate with gemcitabine. There was also more vomiting, fatigue and diarrhea with the three-drug regimen.

However, the results make it worth considering the three-drug regimen for patients who are robust enough to tolerate it. There was a 32 percent response rate compared to 9.4 percent in the gemcitabine arm. There was a significant progression-free survival difference — 6.4 months versus 3.3 months with gemcitabine. The most startling result was an 11.1 versus a 6.8-month median survival advantage with the three-drug regimen. This is the first positive Phase III study that we've had in pancreatic cancer in a long time, and I've already incorporated the results into my practice.

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

Investigator comment on the results of PRODIGE 4/ ACCORD 11: FOLFIRINOX versus gemcitabine as first-line treatment of metastatic pancreatic cancer

From a clinical practice point of view, the French study was significant, demonstrating the value of an intensive chemotherapy regimen in advanced pancreatic cancer. This is almost a paradigm shift in this disease for which we've always thought of using relatively nonaggressive chemotherapy.

The Europeans did a small, Phase II study some years ago in pancreatic cancer and demonstrated some interesting activity with this three-drug regimen. Based on that they finally launched this Phase III study.

Considering how many negative studies we've had in pancreatic cancer, they dramatically showed a greater than four-month improvement in median survival with this three-drug regimen. So the median survival on gemcitabine was 6.8 months, which is fairly typical for this disease and the median survival for FOLFIRINOX was 11.1 months. That is a substantial improvement and certainly beyond what has been seen with any other regimen in pancreatic cancer.

Interview with Malcolm J Moore, MD, June 21, 2010

Phase III Study of First-Line XELOX Plus Bevacizumab (BEV) for 6 Cycles Followed by XELOX Plus BEV or Single Agent (s/a) BEV as Maintenance Therapy in Patients (pts) with Metastatic Colorectal Cancer (mCRC): The MACRO Trial

Tabernero J et al.

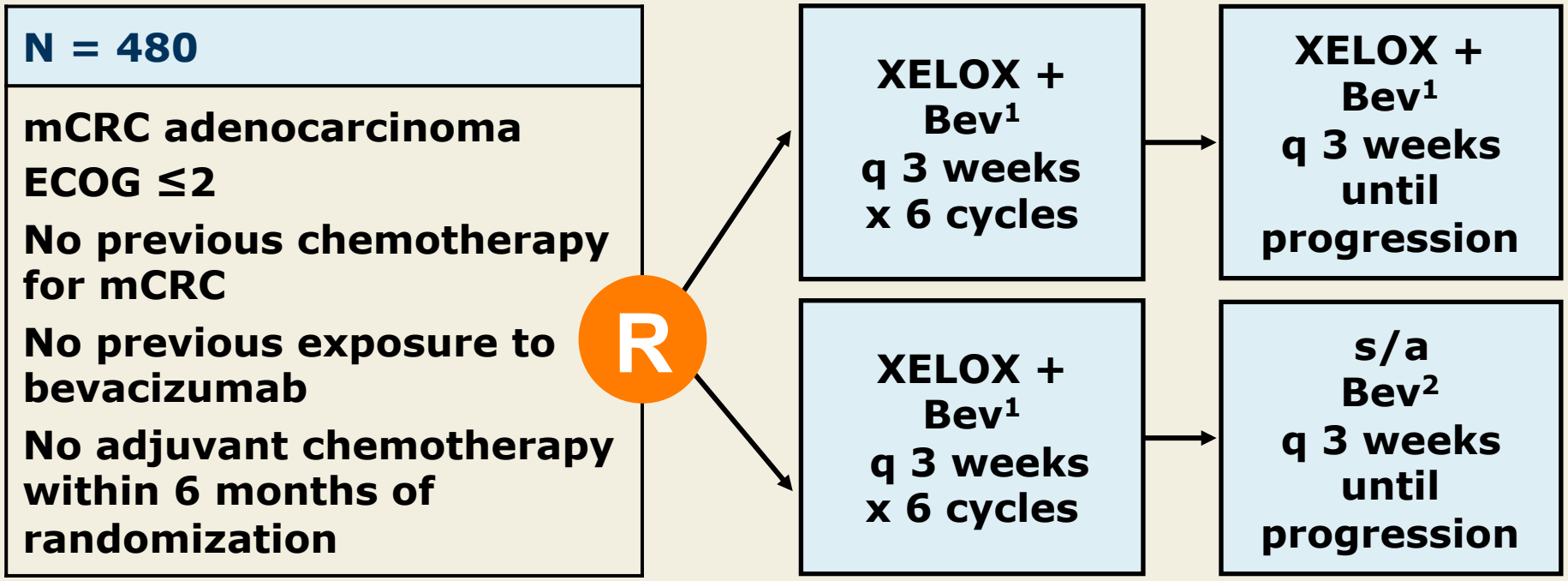
Proc ASCO 2010;Abstract 3501.

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.

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

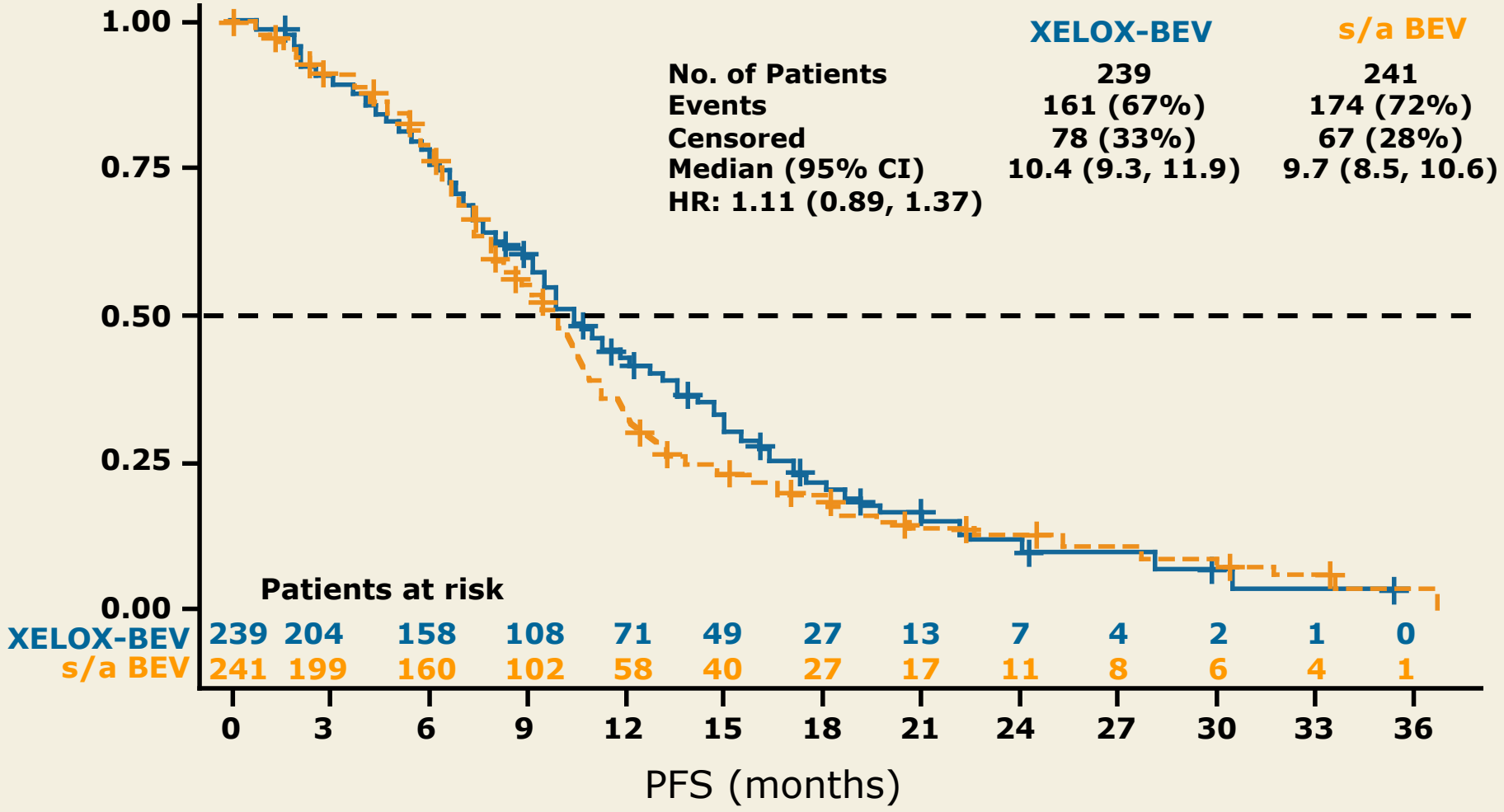
Tabernero J et al. *Proc ASCO* 2010;Abstract 3501.

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.

Median Progression-Free Survival



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

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.

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.

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 in favor of continuing bevacizumab, but the 95-percent confidence interval included 1.37. 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

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

Neoadjuvant FOLFOX with Bevacizumab but without Pelvic Radiation for Locally Advanced Rectal Cancer

Schrag D et al.

Proc ASCO 2010;Abstract 3511.

Introduction

- Standard therapy for locally advanced rectal cancer is 5-FU-based chemotherapy combined with radiation therapy and followed by surgery and adjuvant chemotherapy.
- Although pelvic XRT nearly eliminates the risk of local recurrence (LR), it can be associated with long-term adverse effects on bowel, bladder and sexual functions and can induce myelosuppression.
- Improvements in systemic chemotherapy for patients with Stage III colon cancer and in surgical techniques for patients with rectal cancer have improved patient outcomes.
- **Current study objective:**
  - Assess the feasibility of achieving R0 resection with neoadjuvant FOLFOX plus bevacizumab administered without pelvic XRT in patients with newly diagnosed, locally advanced rectal cancer.

Schrag D et al. *Proc ASCO* 2010;Abstract 3511.

Pilot Study Design

Accrual: 32

Eligibility (N = 30)

Newly diagnosed clinical stage II or III rectal adenocarinoma

uT2N1-2 or uT3N0-2 primary rectal tumor

Candidate for lower anterior resection, FOLFOX and bevacizumab (Bev)

→ **FOLFOX + Bev**
FOLFOX + Bev x 4
→ FOLFOX x 2

→ Patients with progressive or stable disease → XRT + 5-FU

→ Patients with clinical regression → Surgery*

*Post-operative treatment at discretion of physician. FOLFOX x 6 recommended; no post-operative Bev provided.

XRT = radiation therapy

Schrag D et al. *Proc ASCO* 2010;Abstract 3511.

Results (Mean Follow-Up 18.2 Months)

Event Rate	N	%
R0 resection — all pts	32/32	100
R0 resection, on study	30/30	100
Pts needing pre-op pelvic XRT	0/30	0
Pathologic complete response	8/30	27
Deaths	1/30	3
LR rate	0/30	0
Distant recurrence — all lung	3/30	10

Schrag D et al. *Proc ASCO* 2010;Abstract 3511.

Conclusions

- Neoadjuvant FOLFOX-based chemotherapy without XRT does not appear to compromise the R0 resection rate in patients with locally advanced rectal cancer not requiring abdominoperineal resection.
  - R0 resection rate, all patients accrued (n = 32): 100%
  - R0 resection rate, patients on study (n = 30): 100%
- The pathologic complete response (CR) rate was 27% (8/30 patients).
- These data suggest that appropriately selected patients with locally advanced rectal cancer may forego pelvic XRT without adversely affecting R0 resection and pathologic CR rates.
- Based on these preliminary results, a cooperative group study is planned to examine neoadjuvant FOLFOX without XRT in patients with locally advanced rectal cancer.

Schrag D et al. *Proc ASCO* 2010;Abstract 3511.

Investigator comment on the results of a study of neoadjuvant FOLFOX/bevacizumab without radiation therapy for locally advanced rectal cancer

The standard treatment approach for most patients with locally advanced rectal cancer is neoadjuvant chemoradiation therapy. Most acknowledge that radiation therapy is probably the more toxic component of this treatment, particularly the long-term side effects. I have patients who have radiation proctitis, which is nasty and leads to pain, constant diarrhea and sphincter dysfunction. It would be a paradigm shift if we could utilize highly active systemic therapy without radiation therapy.

Memorial Sloan-Kettering Cancer Center had two interesting pilot studies — one with FOLFOX with bevacizumab and one with FOLFOX alone — and in their series, they had an approximately 30 percent pathologic complete response rate for patients with mid- or higher-rectum adenocarcinomas without radiation therapy, which is as good as it gets when you talk about 5-FU-based neoadjuvant chemoradiation therapy. The critical issue this raises in rectal cancer is the importance of adequate imaging. It is imperative to identify patients who are good candidates — those with T3N0, and perhaps T3N1 disease, but definitely not more than that.

Both ACOSOG and CALGB have proposals in their portfolio right now to test this strategy prospectively in a multicenter setting.

Interview with Axel Grothey, MD, July 9, 2010

Investigator comment on the results of a study of neoadjuvant FOLFOX/bevacizumab without radiation therapy for locally advanced rectal cancer

This study is a potential game changer. The Memorial Sloan-Kettering Group speculated that there were some patients who were currently receiving chemoradiation therapy for rectal cancer who didn't need it. We all agree on that concept, but the challenge is in figuring out which patients don't need radiation therapy to avoid putting them at risk.

The Memorial group treated about 30 patients, and they were aggressive in monitoring them. They did baseline CT scans and pelvic scans and did MRI in the interim to make sure patients had responding disease. If the patients' disease was responding, they were treated essentially with four courses of chemotherapy. The patients went to surgery, and if they had an R0 or a resection of all known disease, that was it. They didn't receive radiation therapy. By all accounts this was a positive study, which suggests that radiation therapy is not necessary for every patient. This is huge because it spares patients a lot of toxicity, but physicians should not take it as a carte blanche to practice this outside of clinical trials, which are currently planned in the cooperative group setting.

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

Cetuximab with Chemotherapy (CT) as First-Line Treatment for Metastatic Colorectal Cancer (mCRC): Analysis of the CRYSTAL and OPUS Studies According to KRAS and BRAF Mutation Status

Bokemeyer C et al.

Proc ASCO 2010;Abstract 3506.

Background

- Cetuximab (Cmab) added to chemotherapy (CT) as first-line treatment for patients with mCRC and KRAS wild-type (wt) tumors improved efficacy (CRYSTAL study, *NEJM* 2009;360:1408; OPUS study, *JCO* 2009;27:663).
- BRAF may be an additional biomarker for CRC:
  - BRAF gene mutations (mt) were detected in 8% of CRC tumors (*JCO* 2010;28:466).
  - BRAF mt are suggested to be predictive of Cmab efficacy in pre-treated patients with CRC (*JCO* 2008;26:5705).
- **Current study objective:**
  - To investigate the efficacy of Cmab in patients from CRYSTAL and OPUS trials according to KRAS and BRAF mutation status.

Bokemeyer C et al. *Proc ASCO* 2010;Abstract 3506.

Pooled Analyses: Overall Response Rate

Patient Group	ORR	*p*-value
KRAS wt CT (n = 447) Cmab + CT (n = 398)	 38.5% 57.3%	<0.0001
KRAS wt/BRAF wt CT (n = 381) Cmab + CT (n = 349)	 40.9% 60.7%	<0.0001
KRAS wt/BRAF mt CT (n = 38) Cmab + CT (n = 32)	 13.2% 21.9%	0.4606

ORR = overall response rate

Bokemeyer C et al. *Proc ASCO* 2010;Abstract 3506.

Pooled Analyses: Survival Data

Patient Group	Median OS	HR for OS (*p*-value)	Median PFS	HR for PFS (*p*-value)
KRAS wt				
CT (n = 447)	19.5 mos	0.81 (0.0062)	7.6 mos	0.66 (<0.0001)
CT + Cmab (n = 398)	23.5 mos		9.6 mos	
KRAS wt/BRAF wt				
CT (n = 381)	21.1 mos	0.84 (0.041)	7.7 mos	0.64 (<0.001)
CT + Cmab (n = 349)	24.8 mos		10.9 mos	
KRAS wt/BRAF mt				
CT (n = 38)	9.9 mos	0.63 (0.079)	3.7 mos	0.69 (0.267)
CT + Cmab (n = 32)	14.1 mos		7.1 mos	

OS = overall survival; PFS = progression-free survival

Bokemeyer C et al. *Proc ASCO* 2010;Abstract 3506.

Conclusions

- This pooled analysis confirms that the addition of Cmab to CT in first-line therapy for patients with mCRC and KRAS wt tumors achieves a statistically significant improvement in efficacy compared to CT alone.
- The best outcome was observed in patients with KRAS wt/BRAF wt tumors (90% of KRAS wt patients).
- Based on these results, BRAF mutation status does not appear to be a relevant predictive biomarker for use of Cmab in first-line therapy for mCRC.
  - BRAF mt appears to be an indicator of poor prognosis.
  - However, the sample size may be too small to be reliable.

Bokemeyer C et al. *Proc ASCO* 2010;Abstract 3506.

Investigator comment on the analysis of CRYSTAL and OPUS according to K-ras and B-raf mutation status

The CRYSTAL and the OPUS studies added cetuximab to either FOLFOX or FOLFIRI. OPUS study was a randomized Phase II study and CRYSTAL was a randomized Phase III study. The investigators pooled their data in order to tease out some issues that related to the mutation status of the tumors.

Interestingly, a number of people jumped on the notion that we ought to be performing B-raf testing routinely as we do K-ras testing. As it turns out, this analysis suggests that you can do that and learn about the prognostic features of having a B-raf mutation. Patients who have B-raf mutations in their tumors can still respond to cetuximab. So one shouldn't use B-raf mutation status as a “go/no-go” factor for whether or not to use cetuximab for these patients.

B-raf does carry an adverse prognosis, and response rates were about a third for patients with the B-raf mutation compared to those with B-raf wild-type tumors. So patients with B-raf mutations fare poorly, but they still fared better when cetuximab was added to chemotherapy than when chemotherapy was administered alone.

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

Investigator comment on the analysis of CRYSTAL and OPUS according to K-ras and B-raf mutation status

Two interesting findings emerged from this analysis. First, B-raf is hugely prognostic. Patients with B-raf mutations live about a year less than patients without B-raf mutations, which I thought was shocking. We have always searched for a good prognostic marker in colon cancer, and now we have a marker, which identifies seven to eight percent of patients with a very poor prognosis. Personally, I test for B-raf mutations because this influences the way I approach a patient in terms of stop-and-go strategies. For patients with B-raf mutations, I have to be alert and cannot as easily consider stop-and-go and maintenance therapies.

Second, there was still a numerical benefit for the addition of cetuximab to chemotherapy in terms of response rate, progression-free survival and overall survival, which may refute the initial idea that a mutation in B-raf is a negative predictive marker like K-ras mutations. So my personal preference, if I have a patient with a B-raf mutation, is not to use cetuximab or panitumumab in an earlier-line setting. Would I use it in a last-line setting when the patient's back is against the wall? Based on these data, I might consider that.

Interview with Axel Grothey, MD, July 9, 2010

Adjuvant mFOLFOX6 with or without Cetuximab in Patients with KRAS Wild-Type or KRAS Mutant Resected Stage III Colon Cancer: Results from NCCTG Intergroup Phase III Trial N0147

Goldberg RM et al.
Proc ASCO 2010;Abstract 3508.

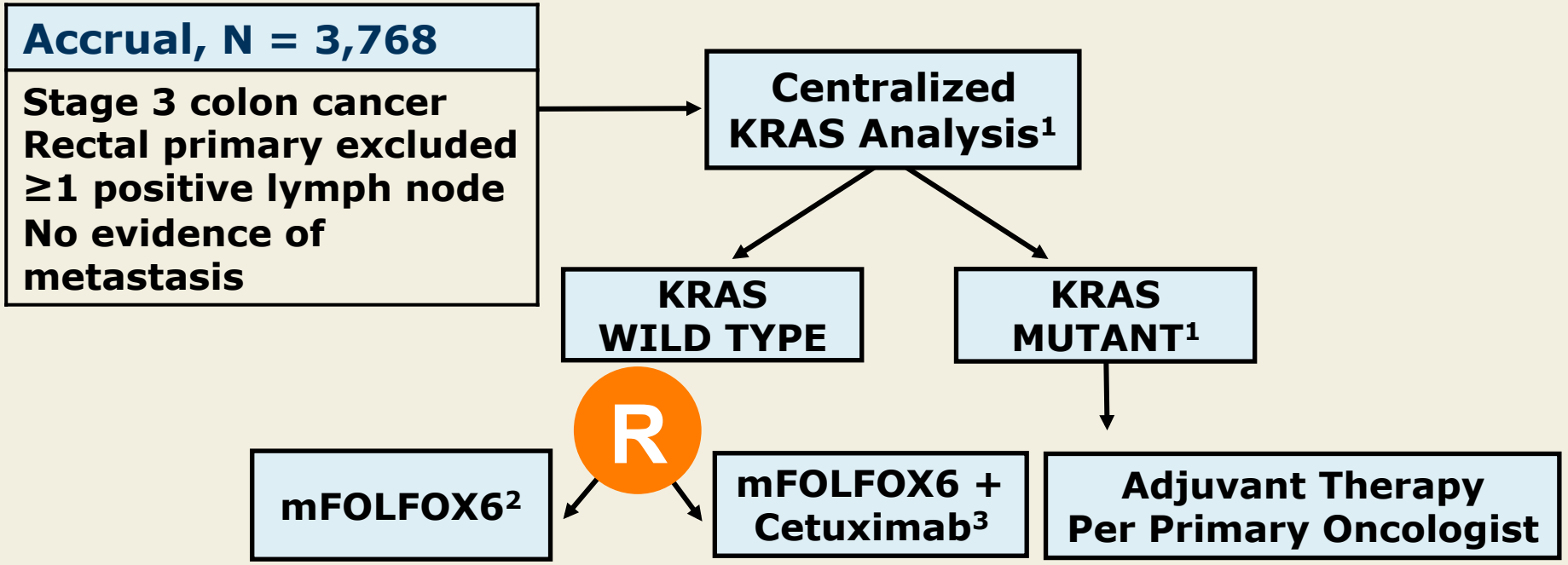
Alberts SR et al.
Proc ASCO 2010;Abstract CRA3507.

Background

- FOLFOX is standard adjuvant therapy and improves disease-free survival and OS in Stage III colon cancer (*JCO* 2009;27:3109).
- Combination of EGFR antibody and chemotherapy demonstrates improved outcome in metastatic colon cancer.
- KRAS wild type was established as a predictive marker for the addition of cetuximab to FOLFOX4 in Stage IV colon cancer (*JCO* 2009;27:663) leading to an N0147 amendment requiring prospective KRAS testing.
- **Current study objectives:**
  - Safety and efficacy of cetuximab added to mFOLFOX6 in patients with:
    - Colon cancer with KRAS wild type present
    - Colon cancer with KRAS mutation present

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508; Alberts SR et al. *Proc ASCO* 2010;Abstract CRA3507.

N0147 Final Design



[1] 717 patients with KRAS mutation were enrolled before an amendment requiring prospective KRAS testing. Patients who were enrolled pre-amendment had KRAS status analyzed retrospectively from paraffin-embedded blocks.

[2] mFOLFOX6 = Oxaliplatin 85 mg/m^2 d1, leucovorin 400 mg/m^2, 5-FU 400 mg/m^2 bolus IV d1, 5-FU 2,400 mg/m^2 d 1-2 (over 46 hours) every 2 wk

[3] Cetuximab 400 mg/m^2 loading dose, then 250 mg/m^2 qwk

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508; Alberts SR et al. *Proc ASCO* 2010;Abstract CRA3507.

Efficacy Endpoints

KRAS Wild Type (23-mo follow-up)	FOLFOX (n = 902)	FOLFOX + Cetuximab (n = 945)	Hazard Ratio	*p*-value
3-Year Disease-Free Survival	75.8%	72.3%	1.2	0.22
3-Year Overall Survival	87.8%	83.9%	1.3	0.13

KRAS Mutant (22.4-mo follow-up)	FOLFOX (n = 374)	FOLFOX + Cetuximab (n = 343)	Hazard Ratio	*p*-value
3-Year Disease-Free Survival	67.2%	64.2%	1.2	0.13
3-Year Overall Survival	88.0%	80.4%	1.5	0.12

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508; Alberts SR et al. *Proc ASCO* 2010;Abstract CRA3507.

Select Grade 3+ Adverse Events

Adverse Event	KRAS Wild Type		KRAS Mutants	
	FOLFOX (n = 883)	FOLFOX + Cetuximab (n = 919)	FOLFOX (n = 364)	FOLFOX + Cetuximab (n = 339)
Paresthesias	9%	7%	13%	9%
Neutropenia (Grade 4+)	10%	11%	12%	13%
Rash	0.1%	8%	0%	9%
Diarrhea	8%	15%	8%	15%
Nausea	3%	4%	2%	6%
Vomiting	3%	3%	3%	5%
Mucositis	2%	7%	3%	7%

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508.

Conclusions

- Cetuximab does not add benefit when added to adjuvant FOLFOX in patients with Stage III colon cancer and either KRAS wild type or KRAS mutation.
- Based on analysis of idealized patients (aged <70 years and with ≥80% dose intensity achieved), the failure of cetuximab added to FOLFOX is not primarily due to lower dose intensity of 5-FU and oxaliplatin when cetuximab was added (data not shown).
- Potential Explanations:
  - Related to tumor biology, cetuximab treatment of KRAS mutants may drive chemotherapy resistance
  - Overall decreased tolerance with addition of cetuximab
  - Lessened ability in older patients (≥70 years) to complete therapy with adjuvant FOLFOX when cetuximab was added (data not shown)

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508; Alberts SR et al. *Proc ASCO* 2010;Abstract CRA3507.

Investigator comment on the results of NCCTG-N0147: mFOLFOX6 with or without cetuximab for Stage III colon cancer

For NCCTG-N0147, we split the analysis, because we wanted to focus first on the entire group of patients and then on those patients with the K-ras mutations. Initially, the randomization was to FOLFOX with or without cetuximab for "all comers," but once we became aware of the importance of K-ras status, we restricted enrollment to patients with K-ras wild-type tumors.

The bottom line is there was no overall value to the addition of cetuximab to chemotherapy in the entire population or in those patients with K-ras wild-type tumors. Unfortunately, there was a detriment when cetuximab was used in patients who were over 70 years old.

Perhaps more startling, for patients with K-ras mutations there was a statistically worse outcome among those who received cetuximab. We would not have predicted this outcome. In some manner that we do not understand, cetuximab interfered with the efficacy of chemotherapy. On the positive side, we did have tumor block requirements for enrollment, so hopefully we can unravel this unexpected finding.

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

Investigator comment on the results of NCCTG-N0147: mFOLFOX6 with or without cetuximab for Stage III colon cancer

This study was started about seven years ago when nobody talked about K-ras status. In the end, the primary endpoint was adjusted to evaluate FOLFOX with or without cetuximab in patients with K-ras wild-type tumors. I was shocked when I saw the data because I believed we had our "HER2 in breast cancer." We had our K-ras-enriched population and a drug like cetuximab, which had clear activity in colon cancer. We knew the population that should be treated with cetuximab and that this should work as adjuvant therapy. It failed miserably. We did not see benefit in patients with K-ras wild-type or mutant tumors. If anything, we observed a detrimental effect from cetuximab, which was pronounced in the elderly and those with K-ras mutations.

With the elderly, we probably compromised the dose of chemotherapy over time. In those with K-ras mutant tumors, we've seen more recent evidence in mCRC that the addition of cetuximab to an oxaliplatin-based regimen interferes with the activity of the underlying chemotherapy.

In the end, this was a disturbing and disappointing outcome. The question is, where do we go from here? I believe we are all pretty much at a loss right now.

Interview with Axel Grothey, MD, July 9, 2010

AVAGAST: A Randomized, Double-Blind Placebo-Controlled, Phase III Study of First-Line Capecitabine and Cisplatin + Bevacizumab or Placebo in Patients with Advanced Gastric Cancer (AGC)

Kang Y et al.

Proc ASCO 2010;Abstract LBA4007.

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.

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.

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.

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.

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.

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

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