



EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 41st American Society of Clinical Oncology (ASCO) Annual Meeting, held May 13–17, 2005 in Orlando, Florida. Leading Canadian experts offer commentary and clinical interpretations.

Colorectal cancer

HIGH-DOSE BEVACIZUMAB IMPROVES SURVIVAL WHEN COMBINED WITH FOLFOX4 IN PREVIOUSLY TREATED ADVANCED COLORECTAL CANCER: RESULTS FROM THE EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) STUDY E3200. (ABSTRACT 2)

Investigators: B.J. Giantonio et al.

In the Eastern Cooperative Oncology Group (ECOG) study E3200, 829 patients were randomized to receive high-dose bevacizumab (10 mg/kg IV every 2 weeks) either alone or in combination with FOLFOX4 (oxaliplatin 85 mg/m² intravenous [IV] on Day 1 + leucovorin 200 mg/m² IV over 2 hours + 5-fluorouracil 400 mg/m² by IV bolus, followed by 5-fluorouracil 600 mg/m² by continuous IV) given every 2 weeks. Another treatment arm receiving bevacizumab alone was closed just before completion of enrollment due to lack of efficacy. Eligible patients had not received prior bevacizumab, had undergone chemotherapy with fluoropyrimidines and an irinotecan-based regimen, and scored 0–2 on the ECOG performance scale.

At median followup of 28 months, patients receiving combined high-dose bevacizumab and FOLFOX4 had improved overall survival (12.9 months vs 10.8 months, $p = 0.0018$) and progression-free survival (7.2 months vs 4.8 months, $p < 0.0001$) compared to those receiving FOLFOX4 alone (Table 1). Overall tumour response was seen in 21.8% vs 9.2% of patients,

complete response in 1.9% vs 0.7%, and stable disease in 51.7% vs 45.0% ($p < 0.0001$ for all response outcomes). The combination was well tolerated, although patients receiving the bevacizumab + FOLFOX4 combination had more hypertension, bleeding, vomiting, neuropathy and bowel perforation compared to those receiving FOLFOX4 alone.

TABLE 1. Survival results with high-dose bevacizumab + FOLFOX4 vs FOLFOX4 alone in 829 patients with advanced colorectal cancer

Endpoint	bevacizumab + FOLFOX4	FOLFOX4	hazard ratio	p value
Median progression-free survival	7.2 months	4.8 months	0.64	$p < 0.0001$
Median overall survival	12.9 months	10.8 months	0.76	$p = 0.0018$

COMMENTARY: Ralph Wong, MD, FRCPC, medical oncologist, St-Boniface General Hospital; Assistant Professor, University of Manitoba, Winnipeg, MB

The ECOG 3200 study confirms that bevacizumab is effective not only as first-line treatment in patients with metastatic colorectal cancer but also as second-line treatment, i.e. for those whose disease has progressed after irinotecan-based therapy. It indicates that this medication is active in combination with both irinotecan and oxaliplatin. These results

combined with last year's report on bevacizumab with irinotecan, fluorouracil, and leucovorin by Hurwitz et al in the *New England Journal of Medicine*¹ and the recent publication by Kabbinavar et al in the *Journal of Clinical Oncology*,² showing efficacy with 5-fluorouracil and leucovorin, tell us that bevacizumab provides a pan-effect in colorectal

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cancer. Used with either fluoropyrimidines, irinotecan or oxaliplatin, either in first- or second-line treatment, this drug is effective in prolonging survival.

Of concern is the increased risk of arterial thrombosis incurred by use of bevacizumab. ECOG 3200 confirmed a doubling of the incidence of heart attacks and strokes, and an increased risk of GI perforation. The side effects will likely be more of an issue in the adjuvant setting, where their risks must be balanced against the potential for cancer cure.

When bevacizumab becomes available in Canada, perhaps in November or December 2005, hopefully the pharmacology and therapeutics committees of each province will find the data strong enough to recommend its adoption. The significant cost of the medication will be a concern, however.

UPCOMING RESEARCH

The use of bevacizumab in metastatic treatment raises the very important question of whether it will be effective in the adjuvant setting, where the aim is to cure rather than to prolong median survival. A related question is whether combining bevacizumab and cetuximab will increase overall survival. A series of trials is planned to address these issues.

The US intergroup will soon be starting a Phase III trial testing the efficacy of chemotherapy combined with bevacizumab, cetuximab or both monoclonal antibodies in metastatic colorectal cancer. Once again, the issue of cost will be raised, as cetuximab is also very expensive. Results presented at last May's ASCO meeting by Saltz et al of a study in which patients with irinotecan-refractory disease received a combination of bevacizumab + cetuximab with or without irinotecan suggest greater efficacy for the combination than would have been expected from either alone.³ The AVANT trial, sponsored by Hoffmann-La Roche, will look at the effects of adding bevacizumab to oxaliplatin-based therapy for patients with high-risk Stage II–III colorectal cancers.

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3. Saltz LB, Lenz H, Hochster H et al. Randomized Phase II Trial of Cetuximab/Bevacizumab/Irinotecan (CB1) versus Cetuximab/Bevacizumab (CB) in Irinotecan-Refractory Colorectal Cancer. *Proc Am Soc Clin Oncol* 2005;23:248s. Abstract 3508.

Pancreatic cancer

ERLOTINIB PLUS GEMCITABINE COMPARED TO GEMCITABINE ALONE IN PATIENTS WITH ADVANCED PANCREATIC CANCER. A PHASE III TRIAL OF THE NATIONAL CANCER INSTITUTE OF CANADA CLINICAL TRIALS GROUP [NCIC-CTG]. (ABSTRACT 1)

Investigators: M. Moore et al.

This study randomized 569 patients with advanced pancreatic adenocarcinoma to receive gemcitabine 1000 mg/m² IV weekly x 7 for 7 out of 8 weeks, then weekly x 3 for 3 out of 4 weeks, plus either erlotinib 100 mg per day or placebo. Enrolled subjects had either unresectable disease or had experienced postsurgical recurrence, and had not undergone prior systemic chemotherapy other than that given concurrently with radiation therapy. Cross-sectional imaging was performed every 8 weeks to evaluate disease status. In 48 patients the dose of erlotinib was increased to 150 mg during the study. At 1-year followup, 24% of the patients receiving erlotinib were

still alive, vs 17% of those taking placebo. Both overall survival and progression-free survival were higher in the erlotinib group (Table 2). Complete response, partial response or stable disease was observed in 57% of patients taking erlotinib (9% complete or partial

response) vs 49% of those on placebo (8% complete or partial response). More Grade 1–2 rash, diarrhea and hematologic toxicities were seen in patients receiving erlotinib, but the rates of Grade 3–4 toxicities were similar in both arms.

TABLE 2. Survival outcomes at 1 year in 569 patients receiving gemcitabine plus erlotinib vs placebo

	erlotinib + gemcitabine	placebo + gemcitabine	hazard ratio	p value
Overall survival	6.37 months	5.91 months	0.81	p = 0.025
Progression-free survival	3.75 months	3.55 months	0.76	p = 0.003

COMMENTARY: Sharlene Gill, MD, MPH, FRCPC, Assistant Professor of Medicine, Division of Medical Oncology, British Columbia Cancer Agency, Vancouver, BC

Each year in Canada, approximately 3500 people are diagnosed with pancreatic cancer, and an equal number die of this very serious malignancy. Gemcitabine was

demonstrated to be superior to 5-fluorouracil in treating advanced disease, with improved clinical response and a modest improvement in survival.¹ As shown in Table 3,

TABLE 3. Negative Phase III trials of combination therapy vs gemcitabine alone in pancreatic adenocarcinoma

Experimental arm	n	overall survival (p value)
Gemcitabine + 5FU ²	327	6.7 vs 5.4 months (p = 0.09)
Gemcitabine + Irinotecan ³	342	6.3 vs 6.6 months (p = 0.79)
Gemcitabine + cisplatin ^{4,5}	107	30 vs 20 weeks (p = 0.43)
	195	8.3 vs 6.0 months (p = 0.12)
Gemcitabine (FDR*) + oxaliplatin ⁶	326	9.0 vs 7.1 months (p = 0.13)
Gemcitabine + pemetrexed ⁷	565	6.2 vs 6.3 months (p = 0.85)
Gemcitabine + exatecan ⁸	349	6.7 vs 6.2 months (p = 0.52)
Gemcitabine + tipifarnib ⁹	688	192 vs 182 days (p = 0.75)
Gemcitabine + marimastat ¹⁰	239	165 vs 164 days (p = 0.95)

*Fixed Dose Rate

advanced pancreatic cancer. But is the outcome clinically meaningful? The small survival benefit needs to be interpreted in the context of a detailed analysis of pharmacoeconomic and clinical benefits, as well as toxicity. Strategies to identify which patients are most likely to respond to anti-EGFR therapies would be of great value. In practice, these results will likely not alter our current standard of care, i.e. gemcitabine monotherapy. They do, however, advance the hope that ongoing and future investigations of combination cytotoxic and targeted therapeutics will yield incremental improvements in the survival of patients with pancreatic cancer.

a number of well-designed randomized trials evaluating the efficacy of gemcitabine in combination with other cytotoxic and biologic therapies have subsequently been completed. Disappointingly, no trial has yet demonstrated a statistically significant survival advantage for combination therapy, so gemcitabine monotherapy remains the accepted standard of care for the palliative management of advanced pancreatic adenocarcinoma.

THE FIRST ADVANCE IN COMBINATION TREATMENT

The current study, NCIC.PA3, was an international, randomized, placebo-controlled trial led by the National Cancer Institute of Canada (NCIC)–Clinical Trials Group. It examined the survival efficacy of adding erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), to standard gemcitabine chemotherapy for patients with locally advanced or metastatic pancreatic adenocarcinoma. Tumour EGFR positivity was not an eligibility requirement for enrollment. Patients receiving erlotinib had statistically significant improvements in overall survival, the primary endpoint, and in the secondary endpoint of progression-free survival. No significant differences were observed in response rates, Grade 3–4 toxicities or global quality of life. In preplanned subgroup analyses, the effect of erlotinib appeared to be more pronounced in metastatic disease and in older, poor performance-status patients. Among the 162 subjects (30%) with tumour available for EGFR analysis, immunohistochemistry identified 53% as EGFR-positive. No differences in survival or erlotinib efficacy related to EGFR status were observed. Skin rash, a toxicity of erlotinib therapy, was associated with improved survival.

In terms of internal and external validity, this was a well-conducted trial in a generalizable study population, and it showed a true, statistically significant benefit. While the absolute improvement in survival is modest, it is the first positive randomized trial of combination therapy in

OTHER APPROACHES

A North American Intergroup trial led by the Southwest Oncology Group (SWOG) is examining an alternate anti-EGFR approach using cetuximab, a chimeric monoclonal antibody to the EGFR receptor. Currently accruing patients with advanced pancreatic cancer, this trial randomly assigns them to treatment with gemcitabine with or without cetuximab. Pursuing the paradigm of multitargeted combination therapies, Hoffman-La Roche is sponsoring the international randomized AVITA trial of gemcitabine and erlotinib with or without bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor.

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Breast cancer

E2100: A RANDOMIZED PHASE III TRIAL OF PACLITAXEL VERSUS PACLITAXEL PLUS BEVACIZUMAB AS FIRST-LINE THERAPY FOR LOCALLY RECURRENT OR METASTATIC BREAST CANCER.

Investigators: K.D. Miller et al.

E2100 evaluated the role of bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Bevacizumab was given in combination with paclitaxel vs paclitaxel alone as first-line therapy in 715 women with locally recurrent or metastatic breast cancer. The median age of participants was 55 years, approximately 40% had been disease-free for 2 years or less and two-thirds had received prior adjuvant chemotherapy. Bevacizumab (10 mg/kg) was given intravenously on Days 1 and 15 and paclitaxel (90 mg/m²) was given weekly on Days 1, 8 and 15. Women with HER2-positive (HER2+) breast cancers were included only if they had received prior treatment with

trastuzumab or had a condition for which trastuzumab was contraindicated. The first planned interim analysis, after 270 events, yielded an overall response rate (ORR) of 28.2% in women receiving paclitaxel and bevacizumab compared to 14.2% in those receiving paclitaxel alone ($p < 0.0001$). Progression-free survival (PFS), the primary endpoint, was 10.97 months in the combination arm vs 6.11 months in the paclitaxel-only arm with a hazard ratio (HR) of 0.50 ($p < 0.001$). Overall survival (OS) appeared to be improved with a HR of 0.67 ($p = 0.01$).

Significant Grade 3–4 toxicities in those treated with bevacizumab were hypertension (13.3% vs 0%) and

proteinuria (2.4 vs 0%). Grade 3–4 thromboembolic complications occurred in 1.2% of patients in both groups. Incidence of bleeding was 0.9% in the bevacizumab recipients and 0% in those receiving paclitaxel alone, a difference that was not statistically significant. Grade 3 peripheral neuropathy was increased, however, in the paclitaxel + bevacizumab arm (19.9% vs 13.6%). Fatigue, neutropenia and decreased left ventricular ejection fraction rates were the same in both groups. Correlative studies investigating quality of life, circulating markers such as serum vascular adhesion molecule 1 (VCAM-1) and urine VEGF, primary tumour analysis for VEGF expression and other factors are ongoing.

COMMENTARY: Debjani Grenier, MD, FRCPC, Medical Oncologist, CancerCare Manitoba, St. Boniface General Hospital; Assistant Professor, University of Manitoba, Winnipeg, MB

Angiogenesis plays a key role in the development of breast cancer and subsequent invasion and metastasis. VEGF is a potent stimulator of angiogenesis; bevacizumab is a humanized monoclonal antibody directed against all isoforms of VEGF-A. In a Phase II study of 75 patients with previously-treated metastatic breast cancer,¹ a 9.3% objective response rate to bevacizumab monotherapy was seen and 7% of patients had stable disease for 22 weeks. The current study by Miller et al, presented at an oral session at last May's ASCO meeting (no abstract available) demonstrates significant clinical activity of bevacizumab in combination with paclitaxel compared to paclitaxel alone — with improved response rates, PFS and an early suggestion of improved OS. Patients receiving bevacizumab tolerated it well but experienced significantly increased Grade 3 and 4 hypertension and proteinuria.

KEY CONSIDERATIONS

Given these results, should bevacizumab in combination with paclitaxel be the standard of care for women with metastatic breast cancer? Issues needing resolution prior to precisely defining the role of bevacizumab pertain to the activity of the control arm therapy, results of other studies using bevacizumab, patient selection and toxicities of antiangiogenic therapy.

Results for the control group receiving paclitaxel monotherapy (ORR = 14.2%, PFS = 6.11 months) are

rather low compared to findings in other trials using first-line paclitaxel as well as in trials using other first-line single agents. In the Cancer and Leukemia Group B (CALGB) 9840 study, weekly paclitaxel as first-line treatment achieved an ORR of 40% and time to tumour progression of 9 months.² As the seemingly poor comparator may be heightening bevacizumab's activity in E2100, further studies of this drug in combination with other chemotherapeutic agents are important.

Miller et al conducted a prior study comparing the efficacy of capecitabine with or without bevacizumab in patients with metastatic breast cancer previously treated with an anthracycline and a taxane.³ Although combination therapy significantly increased response rates (19.8% vs 9.1%, $p = 0.001$), no significant differences were seen in PFS (4.86 vs 4.17 months, HR = 0.98) or OS (15.1 vs 14.5 months). Why improved responses did not translate into improved outcomes is unclear, but it should be emphasized that in this trial more than 85% of patients had received at least 1 prior chemotherapy regimen for metastasis and more than one-third had received 2 or more prior regimens. Greater activity of any cancer agent is expected in less heavily pretreated patients. Encouragingly, a study of first-line therapy for metastatic colorectal cancer found that bevacizumab in combination with irinotecan, 5-fluorouracil and leucovorin increased the ORR and prolonged PFS and OS compared to chemotherapy alone.⁴

A key issue in trials of biologic agents is the selection of patients who are most likely to benefit. This is clearly evident in the recently reported impressive results of adjuvant trastuzumab therapy in women with overexpressing HER2 breast cancers. Similarly, other biologic therapies such as gefitinib and erlotinib clearly confer major advantages only to certain specific patients. To date, no factors predicting benefit of bevacizumab have been clearly determined, including VEGF expression — so we eagerly await the analyses of primary tumour samples for factors correlating with response to bevacizumab that are ongoing in many trials, including E2100.

Bevacizumab's significant activity in the E2100 study must be balanced with its toxicities. Optimizing overall quality of life is the main goal of therapy for women with metastatic breast cancer. Approximately 13% of patients receiving bevacizumab in E2100 required intervention for hypertension. Importantly, women with a history of significant proteinuria (more than 500 milligrams in 24 hours) were ineligible for trial entry, based on the finding in Miller et al's prior study³ that those with proteinuria were more likely to develop hypertension while taking bevacizumab. Reassuringly, use of the monoclonal antibody in E2100 did not significantly increase bleeding, thromboembolic events or cardiotoxicity. Patients receiving combined bevacizumab and paclitaxel experienced increased Grade 3 peripheral neuropathy (19.9% vs 13.6%); this likely relates to longer

exposure to paclitaxel in this group given their improved PFS and OS.

ANSWERS AND FURTHER QUESTIONS

E2100 showed that combining bevacizumab with paclitaxel conferred improved ORR, PFS and early OS compared to paclitaxel alone as first-line treatment for metastatic breast cancer. Thus, if upfront treatment with paclitaxel for metastatic breast cancer is being considered, adding bevacizumab seems appropriate. Remaining questions include the role of bevacizumab in combination with other chemotherapy agents, trastuzumab or endocrine therapies; efficacy of bevacizumab as monotherapy; and the cost effectiveness of incorporating bevacizumab into the treatment of metastatic breast cancer. For now, bevacizumab is the first antiangiogenic agent in Phase III trials to show benefit in women with metastatic breast cancer, and we eagerly await studies of this agent in the adjuvant breast cancer setting.

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E2197: PHASE III AT (DOXORUBICIN/DOCETAXEL) VS. AC (DOXORUBICIN/CYCLOPHOSPHAMIDE) IN THE ADJUVANT TREATMENT OF NODE POSITIVE AND HIGH RISK NODE NEGATIVE BREAST CANCER. (ABSTRACT 512)

Investigators: L Goldstein et al.

E2197 was a Phase III, randomized Intergroup trial designed to compare the results of doxorubicin + docetaxel (AT) vs doxorubicin + cyclophosphamide (AC) as adjuvant treatment in women with node-positive or high-risk, node-negative breast cancer. Eligible patients had 1–3 positive nodes or node-negative tumours > 1 cm, and were randomized to 4 cycles of doxorubicin 60 mg/m² + docetaxel 60 mg/m² or doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m². At median followup of 53 months, out of 2889 analyzable patients, 197 of 1444 women receiving the AT combination

had experienced recurrence, vs 212 of the 1445 receiving AC. Despite fewer breast cancer events in the group receiving doxorubicin + docetaxel, the dif-

ferences in disease-free survival (DFS) (Table 4) and OS were not significant. The authors noted that outcomes were better than expected for both regimens.

TABLE 4. Disease-free survival in 2889 women receiving doxorubicin + docetaxel (AT) vs doxorubicin + cyclophosphamide (AC)

Patients	AT	AC	hazard ratio (95% CI)*	p value
Estrogen receptor-positive	90%	90%	0.99 (0.75–1.30)	p = 0.96 (ns)
Estrogen receptor-negative	82%	79%	1.21 (0.92–1.59)	p = 0.17 (ns)
All	87%	87%	1.08 (0.98–1.31)	p = 0.43 (ns)

* HR > 1 favours AT

COMMENTARY: Hagen Kennecke MD, MHA, FRCPC, Medical Oncologist, British Columbia Cancer Agency, Vancouver, BC

This well conducted Phase III trial investigated a logical question: whether the commonly used chemotherapeutic

regimen AC could be improved by substituting docetaxel — an agent with substantial single-agent activity in the

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treatment of metastatic disease — for cyclophosphamide, which has little known activity as a single agent. Many oncologists reserve AC, believed to be equivalent to 6 months of CMF (cyclophosphamide, methotrexate and 5-fluorouracil) chemotherapy¹ but inferior to a 6-month anthracycline regimen,² for what is perceived to be “intermediate-risk” disease. Intermediate-risk breast cancer is usually defined as having a 15% to 25% risk of recurrence and includes tumours that meet the criteria of being 1–1.9 cm in size, node-negative, Grade 1 or 2 HER2-negative, and free of lymphatic or vascular invasion.³


DFS was not significantly different overall nor in any of the estrogen and progesterone receptor (ER, PR) subgroups. In the ER-positive subgroup, survival was remarkably high at 90% in both arms, whereas ER-negative patients fared worse with a DFS of 79% for those on AC vs 82% on AT ($p = 0.17$). Regarding toxicity, the AT recipients had significantly more febrile neutropenia and infection compared to those receiving AC (28% vs 10%). Eighteen patients in the AT group experienced \geq Grade 3 congestive heart failure, compared to 10 of those in the AC group, but incidence was low and the differences were not statistically significant.

The authors cite better-than-expected outcomes in both treatment arms as a possible explanation for the trial’s negative results. The majority of women enrolled were ER-positive or node-negative and fewer events led to a decrease in the power of the trial. A potential reason for this is that enrolling oncologists are likely to choose 6-month anthracycline-based regimens for node-positive and/or ER-negative breast cancer — something that needs to be considered when designing a trial where the control arm is 4 cycles of AC alone.

USEFUL DESPITE NEGATIVE RESULTS

The fact that a significant portion of patients enrolled in this trial meet the criteria for the Genomic Health Oncotype DX gene panel,⁴ (i.e. their tumours were node-negative

and ER-positive) has not escaped the attention of the authors; there are plans to use ECOG 2197 as a training set for validation in ECOG 1199, a trial comparing AC followed by weekly or 3-weekly paclitaxel or docetaxel in women with node-positive breast cancer. This raises the important point that a predictive tool would be very useful to help determine which intermediate-risk patients are at higher risk and would benefit from adjuvant chemotherapy, in contrast to those at lower risk for whom chemotherapy promises minimal benefit. Currently, for those at high risk, the most appropriate chemotherapy regimen is probably 6 months in duration and anthracycline-based, as described in the recent analysis of the Early Breast Cancer Trialists’ Collaborative Group.⁵ Even with predictive tools, however, an intermediate-risk group will likely remain, although significantly diminished in size.

For now, oncologists will likely continue to use AC chemotherapy for the small group of patients perceived to be at intermediate risk of breast cancer recurrence. The results of E2197 do not justify switching to AT chemotherapy but serve as a step in the path to better stratifying patients according to both risk and therapy. 

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