Bevacizumab for the Treatment of Metastatic Breast Cancer

The importance of angiogenesis in cancer biology has been recognized for decades. One of the first angiogenesis-stimulating factors identified was the vascular endothelial growth factor (VEGF). Bevacizumab, a monoclonal antibody, inhibits the activity of VEGF. At the 2005 ASCO meeting, Dr Kathy Miller reported the results from ECOG-E2100, a Phase III randomized trial evaluating the addition of bevacizumab to paclitaxel as first-line therapy in women with metastatic breast cancer. The addition of bevacizumab was found to improve not only the response rate and progression-free survival but also overall survival. These findings have led to the incorporation of bevacizumab in multiple clinical trials, in both the adjuvant and metastatic settings. An update of this important study was presented at the 2005 San Antonio Breast Cancer Symposium.

ECOG-E2100: PACLITAXEL WITH OR WITHOUT BEVACIZUMAB AS FIRST-LINE THERAPY

Efficacy Endpoints	Paclitaxel + bevacizumab (n = 341)	Paclitaxel (n = 339)	*p*-value
Response rate			
All patients	29.9%	13.8%	<0.0001
Measurable disease	37.7%	16.0%	<0.0001
Progression-free survival	11.4 months	6.11 months Hazard ratio = 0.51 (CI: 0.43-0.62)	<0.0001
Overall survival	28.4 months	25.2 months Hazard ratio = 0.84 (CI: 0.64-1.05)	0.12
Safety Results	**Paclitaxel + bevacizumab (n = 350)**	**Paclitaxel (n = 332)**	***p*-value**
Hypertension			
Grade III	15%	2%	
Grade IV	<1%	0%	<0.0001
Thromboembolism			
Grade III	2%	2%	
Grade IV	0%	2%	NS
Bleeding			
Grade III	2%	0%	
Grade IV	<1%	0%	0.02
Proteinuria			
Grade III	1%	0%	
Grade IV	1%	0%	0.002
Neuropathy			
Grade III	22%	17%	
Grade IV	1%	1%	NS

NS = not significant

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 3.

RANDOMIZED PHASE II TRIAL OF METRONOMIC CHEMOTHERAPY ± BEVACIZUMAB

Eligibility	Stage IV disease with no prior chemotherapy for metastatic breast cancer
ARM 1	CM alone*
ARM 2	CM + bevacizumab 10 mg/kg q2wk

C = cyclophosphamide 50 mg PO qd; M = methotrexate 2.5 mg PO BID d1, 2 qwk; * Option to cross over upon disease progression

Best overall response	CM alone (n = 21)		CM + bevacizumab (n = 34)	
	N	Percent	N	Percent
Partial response	2 95% CI: 1-30%	10	10 95% CI: 15-50%	29
Stable disease	8	38	14	41
Progressive disease	9	43	9	26
Not available	2	10	1	3

SOURCE: Burstein HJ et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 4.

USE OF BEVACIZUMAB: A SURVEY OF US ONCOLOGISTS, SEPTEMBER 2005

	BCI (N = 45)	CO (N = 50)
Utilized bevacizumab to treat breast cancer off protocol	73%	4%
Have not utilized bevacizumab but intend to use it	18%	64%
Have not utilized and have no immediate intention to use it	9%	32%

BCI = breast cancer investigators; CO = community oncologists

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

CURRENT OR PROPOSED BREAST CANCER CLINICAL TRIALS EVALUATING BEVACIZUMAB

Protocol ID	Setting	Accrual	Protocol
ECOG-E2104*	Adjuvant	42-202	Dose-dense AC q2wk x 4 + bevacizumab → bevacizumab + paclitaxel q2wk x 4 → bevacizumab q2wk x 18 Dose-dense AC q2wk x 4 → bevacizumab + paclitaxel q2wk x 4 → bevacizumab q2wk x 22
Dana-Farber/ Beth Israel, 05-055*†	Adjuvant	100	Bevacizumab q3wk x 12mo Bevacizumab q3wk + cyclophosphamide d + methotrexate qwk x 6mo → bevacizumab q3wk x 6mo
UCLA-0502123-01	Neoadjuvant	90	Bevacizumab 7.5 mg/kg q3wk → TAC + bevacizumab 7.5 mg/kg q3wk Placebo → TAC + placebo Bevacizumab 15 mg/kg q3wk → TAC + bevacizumab 15 mg/kg q3wk Placebo → TAC + placebo higher dose
UAB-0467	Neoadjuvant	NR	Letrozole + bevacizumab 15 mg/kg q3wk x 18wk
XCaliBr† (ML18527)	Metastatic, first-line	92	Capecitabine + bevacizumab → vinorelbine + bevacizumab Capecitabine + bevacizumab → paclitaxel + bevacizumab
UCLA-0109030-03*	Locoregional relapse/metastatic	3-74	Phase I: Trastuzumab + bevacizumab escalated to maximum tolerated dose (MTD) Phase II: Trastuzumab + bevacizumab at MTD
UCLA-0501049-01	Metastatic	150	Docetaxel q3wk (Docetaxel + bevacizumab 15 mg/kg) q3wk
NCI-05-C-0022	Refractory, Metastatic, Unresectable	3-38	Bevacizumab + sorafenib to MTD → Sorafenib at MTD d1-21 → (Sorafenib d1-21 + bevacizumab d1, 15) q28d → Bevacizumab at MTD d1, 15 → (Sorafenib d1-21 + bevacizumab d1, 15) q28d

NR = not reported; * bevacizumab = 10 mg/kg q2wk; † patients with residual breast cancer following preoperative chemotherapy

SOURCES: NCI Physician Data Query, January 2006; Miller KD. *Breast Cancer Update* Meeting 2005.

SELECT PUBLICATIONS

Burstein HJ et al. **Metronomic chemotherapy with and without bevacizumab for advanced breast cancer: A randomized phase II study.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 4.

Hudis C. **Clinical implications of antiangiogenic therapies.** *Oncology (Williston Park)* 2005;19(4 Suppl 3):26-31.

Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial coordinated by the Eastern Cooperative Oncology Group (E2100).** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 3.

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. ASCO 2005.

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005;23(4):792-9.

Schneider BP, Miller KD. **Angiogenesis of breast cancer.** *J Clin Oncol* 2005;23(8):1782-90.

Traina TA et al. **A phase II trial of letrozole in combination with bevacizumab, an anti-VEGF antibody, in patients with hormone receptor-positive metastatic breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 2030.

ECOG-E2100: PACLITAXEL WITH OR WITHOUT BEVACIZUMAB AS FIRST-LINE THERAPY

The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and increases the objective response rate with minimal increases in toxicity. Future studies in this area should begin to explore the role of bevacizumab in the adjuvant setting and continue to investigate methods to identify those patients who are most likely to benefit from VEGF-targeted therapies.

The next step in this process will activate soon in a trial known as E2104. This adjuvant pilot trial will investigate the safety and feasibility of incorporating bevacizumab into standard adjuvant chemotherapy, using the dose-dense anthracycline followed by paclitaxel regimen, as used in the previous CALGB-9741 trial.

— Kathy D Miller, MD et al. Presentation. ASCO 2005.

ECOG-E2100: SAFETY

As a result of the previous toxicity seen in the lung cancer trial, we had very stringent criteria for discontinuing E2100 if we saw an excess number of patients developing Grade IV hypertension or bleeding. When the trial was initiated, the National Cancer Institute had significant concerns about patient safety as a result of the initial experience with bevacizumab in lung cancer. Fortunately, early analyses demonstrated that was not an issue in breast cancer. The side effects were relatively minimal. Predominantly, we saw mild to moderate increases in blood pressure, which is readily handled from a clinical standpoint. Of course, we'll have to be careful with the hypertension as we move bevacizumab into the adjuvant setting. We also saw a low incidence of serious bleeding. Overall, bevacizumab was a nontoxic addition to chemotherapy.

— George W Sledge Jr, MD.* Breast Cancer Update *2005 (6)

IMPLICATIONS OF E2100

I believe the results of ECOG-E2100 are impressive enough that, in the absence of a contraindication to bevacizumab, I would use it in a first-line setting, optimally in combination with paclitaxel as administered in the study. I doubt that the interaction is specific to paclitaxel and bevacizumab, although I'm well aware that when given with capecitabine in more advanced disease, bevacizumab seemed to be less active. However, I believe that's probably related to the setting rather than the drug.

— Eric P Winer, MD.* Breast Cancer Update *2005 (7)

NEW CLINICAL TRIALS OF BEVACIZUMAB

An ECOG pilot trial of adjuvant bevacizumab, which will be primarily evaluating safety issues, will involve over 200 patients and will open within the next few months. Our belief is that given adequate safety data in the adjuvant setting — which we hope to have within 12 to 18 months — we'll be able to go directly to a large Phase III trial comparing chemotherapy to chemotherapy plus bevacizumab. Of course, many questions can be asked in the adjuvant setting with bevacizumab — which combination chemotherapy or what duration of therapy — and these may require more than one trial to answer. We will also need more than one trial because we'll have to evaluate both HER2-negative and HER2-positive disease.

— George W Sledge Jr, MD.* Breast Cancer Update *2005 (6)

The XCaliBr trial will start very soon. This trial will evaluate newly diagnosed patients — essentially the same group as in the E2100 trial — who need chemotherapy but use capecitabine in combination with bevacizumab. This trial allows but does not require patients to continue bevacizumab after initial progression either with vinorelbine or paclitaxel, at the patients' and investigators' choice. This is a fairly small Phase II trial with only 92 patients, so it will not be definitive. Randomization to continuing bevacizumab or not is not included. That is an open question we need to address quickly.

— Kathy D Miller, MD.* Breast Cancer Update *2005 (7)