ECOG Trial E2100: Paclitaxel Alone or with Bevacizumab

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 not only improve the response rate and progression-free survival but also overall survival. These findings have led to the incorporation of bevacizumab in multiple clinical trials, both in the adjuvant and metastatic settings. An update of this important study will be presented at this meeting.

ECOG-E2100: PHASE III RANDOMIZED TRIAL OF PACLITAXEL WITH OR WITHOUT BEVACIZUMAB AS FIRST-LINE THERAPY IN PATIENTS WITH LOCALLY RECURRENT OR METASTATIC BREAST CANCER

Protocol IDs: ECOG-E2100, CTSU, NCT00028990, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100
Accrual: 715 (Closed)

Eligibility	**Locally recurrent or metastatic breast cancer HER2-positive only if prior treatment with or contraindication to trastuzumab, no prior chemotherapy for metastatic disease, adjuvant taxane allowed if disease-free interval >12 months, PS 0 or 1, no CNS metastases**
ARM 1	**Paclitaxel 90 mg/m^2 (days 1, 8 and 15) + bevacizumab 10 mg/kg (days 1 and 15)**
ARM 2	**Paclitaxel 90 mg/m^2 (days 1, 8 and 15)**

SOURCE: Miller KD et al. Presentation. ASCO 2005.

ECOG-E2100 SAFETY RESULTS

	Paclitaxel + bevacizumab (n = 342)	Paclitaxel (n = 330)
Hypertension*		
Grade III	13%	0%
Grade IV	0.3%	0%
Thromboembolic		
Grade III	1.2%	0.3%
Grade IV	0%	0.9%
Bleeding		
Grade III	0.6%	0%
Grade IV	0.3%	0%
Proteinuria†		
Grade III	0.9%	0%
Grade IV	1.5%	0%
Neuropathy‡		
Grade III	19.9%	13.6%
Grade IV	0.6%	0.6%

* $p < 0.0001$; † $p = 0.0004$; ‡ $p = 0.01$

SOURCE: Miller KD et al. Presentation. ASCO 2005.

ECOG-E2100: FIRST PLANNED INTERIM ANALYSIS OF PRIMARY AND SECONDARY EFFICACY ENDPOINTS

	Paclitaxel + bevacizumab (n = 330)	Paclitaxel (n = 316)	*p*-value
Response rate			
All patients	28.2%	14.2%	<0.0001
Measurable disease	34.3%	16.4%	<0.0001
Progression-free survival	10.97 months	6.11 months	
	Hazard ratio = 0.498 (CI: 0.401-0.618)		<0.001
Overall survival	Hazard ratio = 0.674 (CI: 0.495-0.917)		0.01

SOURCE: Miller KD et al. Presentation. ASCO 2005.

INCORPORATION OF BEVACIZUMAB INTO TREATMENT OF BREAST CANCER: A SURVEY OF US ONCOLOGISTS, SEPTEMBER 2005 (N = 50)

Utilized bevacizumab to treat breast cancer off protocol	4%
Have not utilized bevacizumab but intend to use it	64%
Have not utilized and have no immediate intention to use it	32%
If utilized, for what duration?	
Until disease progression	74%
Beyond disease progression	20%
Other	6%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

CURRENT OR PROPOSED BREAST CANCER CLINICAL TRIALS EVALUATING BEVACIZUMAB

Protocol	Setting	Target 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 daily + methotrexate qwk x 6mo → bevacizumab q3wk x 6mo
UCLA-0502123-01	Neoadjuvant	90	Bevacizumab → TAC + bevacizumab Placebo → TAC + placebo Bevacizumab $^{\text{higher dose}}$ → TAC + bevacizumab $^{\text{higher dose}}$ Placebo $^{\text{higher dose}}$ → TAC + placebo $^{\text{higher dose}}$
CWRU-3100*	Locally advanced	60	Docetaxel + bevacizumab Docetaxel
XCaliBr† (ML18527)	Metastatic, first line	92	Capecitabine + bevacizumab → vinorelbine + bevacizumab Capecitabine + bevacizumab → paclitaxel + bevacizumab
DFCI-03083*	Metastatic	36-66	Metronomic cyclophosphamide/methotrexate + bevacizumab Metronomic cyclophosphamide/methotrexate
NCCTG-N0432†	Metastatic, first line	47	Docetaxel + capecitabine + bevacizumab
UCLA-0109030-03*	Locoregional relapse/ metastatic	3-74	Phase I: Trastuzumab + bevacizumab escalated to maximum tolerated dose (MTD; [closed 11/04]) Phase II: Trastuzumab + bevacizumab at MTD

Metronomic cyclophosphamide = low dose, oral daily days 1-28; metronomic methotrexate = low dose, oral BID days 1, 2, 8, 9, 15, 16, 22, 23
* Bevacizumab = 10 mg/kg q2wk; † bevacizumab = 15 mg/kg q3wk; ‡ patients with residual breast cancer following preoperative chemotherapy

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

SELECT PUBLICATIONS

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

Ignoffo RJ. **Overview of bevacizumab: A new cancer therapeutic strategy targeting vascular endothelial growth factor.** *Am J Health Syst Pharm* 2004;61(21 Suppl 5):21-6.

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.

Rugo H. **Bevacizumab in the treatment of breast cancer: Rationale and current data.** *Oncologist* 2004;9(Suppl 1):43-9.

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

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

...In conclusion, this is a positive study. 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 between 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)