Antiangiogenic Therapy

The importance of angiogenesis in cancer biology has been recognized for decades. One of the first stimulating factors identified was the vascular endothelial growth factor (VEGF). At the 2002 San Antonio Breast Cancer Symposium, Kathy Miller and colleagues reported on the first Phase III randomized trial in breast cancer evaluating the anti-VEGF monoclonal antibody bevacizumab. This ECOG study compared capecitabine alone to capecitabine combined with bevacizumab in heavily pretreated patients with metastatic breast cancer and found a modest response rate advantage to the combination but no improvement in the primary endpoint of time to progression. Another key ECOG study is evaluating bevacizumab combined with paclitaxel in the first-line setting. The hope is that a more significant advantage may be seen in earlier-stage disease, as was observed in the recently reported trial in colorectal cancer in which a marked survival advantage was observed for bevacizumab plus irinotecan and 5-FU/leucovorin (IFL) compared to IFL alone. The first interim efficacy analysis from the ECOG-2100 trial is expected to be reported in early summer of 2005.

EFFICACY OF IFL (IRINOTECAN, 5-FU, LEUCOVORIN) WITH OR WITHOUT BEVACIZUMAB IN METASTATIC COLORECTAL CANCER

Efficacy	Bevacizumab/ IFL (n=402)	IFL/placebo (n=411)	Hazard ratio	*p*-value
Overall survival	20.3 months	15.6 months	0.66	<0.001
Progression-free survival	10.6 months	6.2 months	0.54	<0.001
Response rate	44.8%	34.8%	—	0.004

Following the submission of these results, the FDA granted approval in Feb 2004 for the use of bevacizumab as a first-line treatment for metastatic colorectal cancer.

SOURCE: Hurwitz H et al. *N Engl J Med* 2004;350(23);2335-42.

PHASE III RANDOMIZED TRIAL OF PACLITAXEL WITH OR WITHOUT BEVACIZUMAB IN PATIENTS WITH LOCALLY RECURRENT OR METASTATIC BREAST CANCER

Protocol IDs: E-2100, CTSU
Target Accrual: 316-650 (Closed)

Eligibility	Locally recurrent disease not amenable to resection with curative intent or metastatic disease
ARM 1	Paclitaxel qwk x 3 + bevacizumab q2wk
ARM 2	Paclitaxel qwk x 3

In both arms, treatment repeats q4wk x 18 in the absence of disease progression or unacceptable toxicity.

SOURCE: NCI Physician Data Query, January 2005.

PHASE III RANDOMIZED STUDY OF BEVACIZUMAB WITH CAPECITABINE VERSUS CAPECITABINE ALONE IN WOMEN WITH PREVIOUSLY TREATED METASTATIC BREAST CANCER

Protocol IDs: Genentech-AVF2119g, GUMC-00299, MSKCC-01008, UAB-0028, UAB-F001009003
Accrual: 462 (Closed)

Eligibility	Metastatic breast cancer previously treated with one or two chemotherapy regimens for metastatic disease or no prior chemotherapy for metastatic disease if previously treated with an adjuvant anthracycline and taxane regimen and relapsed within 12 months
ARM 1	Capecitabine (days 1-14) q3wk
ARM 2	Capecitabine (days 1-14) q3wk + bevacizumab (day 1) q3wk

Treatment repeats for up to 35 courses in the absence of disease progression or unacceptable toxicity.

SOURCE: NCI Physician Data Query, January 2005.

EFFICACY AND TOXICITY OF CAPECITABINE PLUS BEVACIZUMAB VERSUS CAPECITABINE ALONE

	Capecitabine	Capecitabine + bevacizumab
Efficacy	**n=230**	**n=232**
Objective response rate	19.1%	30.2%
Duration of response	6.7 months	4.96 months
Progression-free survival	4.2 months	4.9 months
Toxicity	**n=215**	**n=229**
Hypertension (Grade III)	0.5%	17.9%
Thromboembolic	5.6%	7.4%
PE	1.4%	1.3%
DVT	2.3%	6.1%
Bleeding	11.2%	28.8%
Grade ≥III	1.4%	0.4%
Proteinuria	7.4%	22.3%
Cardiac (Grade III or IV)	0.9%	3.1%

SOURCE: Miller K. Presentation. San Antonio Breast Cancer Symposium, 2002.

CLINICAL TRIALS EVALUATING THE ANTI-VEGF BEVACIZUMAB IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH METASTATIC BREAST CANCER

Chair	Protocol ID	Status	Accrual	Study arms
Miller	E-2100, CTSU	Closed	316-650	Bevacizumab q2wk + paclitaxel qwk x 3 vs paclitaxel qwk x 3; treatment repeats q4wk x 18
Wedam	NCI-01-C-0173, NCI-2772	Closed	23	(Bevacizumab + AT + G-CSF q3wk) x 7 → surgery → bevacizumab q3wk x 8
Overmoyer	CWRU-3100, NCI-2722	Open	60	Bevacizumab q2wk, wks 1-8 + T qwk, wks 1-6 vs T qwk, wks 1-6 Patients with stable or responsive disease → surgery → AC x 4
Burstein	DFCI-01013, NCI-2716	Closed	56	Bevacizumab q2wk + vinorelbine qwk; treatment repeats q8wk x 4

A = doxorubicin; C = cyclophosphamide; T = docetaxel

SOURCE: NCI Physician Data Query, January 2005.

SELECT PUBLICATIONS

Browder T et al. **Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer.** *Cancer Res* 2000;60(7):1878-86.

Burstein HJ et al. **Phase II trial of the anti-VEGF antibody bevacizumab in combination with vinorelbine for refractory advanced breast cancer.** *Breast Cancer Res Treat 2002*;Abstract 446.

Eberhard A et al. **Heterogeneity of angiogenesis and blood vessel maturation in human tumors: Implications for antiangiogenic tumor therapies.** *Cancer Res* 2000;60(5):1388-93.

Holash J et al. **New model of tumor angiogenesis: Dynamic balance between vessel regression and growth mediated by angiopoietins and VEGF.** *Oncogene* 1999;18(38):5356-62.

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42.

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. **Phase III trial of capecitabine (Xeloda) plus bevacizumab (Avastin) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane.** *Breast Cancer Res Treat* 2002;Abstract 36.

Moses MA et al. **A role for antiangiogenic therapy in breast cancer.** *Curr Oncol Rep* 2004;6(1):42-8.

CLINICAL TRIALS OF BEVACIZUMAB IN WOMEN WITH METASTATIC BREAST CANCER

I believe the differences in the trial results of bevacizumab in breast cancer and colon cancer were attributable to when patients were treated during the course of the disease — rather than some inherent difference in the biology of the cancers.

Our breast cancer ECOG trial evaluating bevacizumab with capecitabine enrolled patients with advanced disease that was refractory to anthracycline and taxane therapy. Those patients could have received up to two other chemotherapy regimens for metastatic disease if they had received both an anthracycline and a taxane as adjuvant therapy.

Dr Hurwitz's trial of bevacizumab with IFL was conducted in patients with metastatic colon cancer who had not received previous chemotherapy for metastatic disease but could have undergone adjuvant chemotherapy. Likewise, our ECOG-2100 breast cancer trial enrolled patients with breast cancer who had not received chemotherapy for metastatic disease but could have received adjuvant chemotherapy.

Patients were randomly assigned to weekly paclitaxel with or without bevacizumab. The primary endpoint for ECOG-2100 is time to progression.

— Kathy D Miller, MD

IDENTIFYING A TARGET FOR BEVACIZUMAB

I don't view bevacizumab as negative in breast cancer. The capecitabine trial was asking a great deal of bevacizumab in advanced breast cancer, and it showed an increased response rate. Fortunately, an ongoing first-line trial in advanced disease will further elucidate the role of this agent in breast cancer. We're also excited about the potential of bringing bevacizumab into the adjuvant breast cancer setting.

We haven't identified a target for bevacizumab — one that we could use to restrict its use to a subset of the population — but clearly that's a goal. It's often pointed out that if we had conducted the trastuzumab trials on the entire population of patients with breast cancer, we would not have seen an effect. Fortunately, the target could be measured. If we find a target for bevacizumab, the effects may be impressive.

— Norman Wolmark, MD

FUTURE DIRECTIONS WITH BEVACIZUMAB

In an anthracycline- and taxane-refractory setting, adding bevacizumab to capecitabine just about doubles the response rate but does not appear to improve time to progression or overall survival. There is clearly a biologic impact in that setting, but it's not clear that it translates to clinical benefit.

It will be interesting to see whether or not bringing that therapy sooner up front in the metastatic breast cancer setting, as is being done in E-2100, will provide a real clinical benefit, as opposed to simply the response rate benefit we're seeing.

The possibility of adjuvant bevacizumab is certainly reasonable to look at. Approximately 30 to 50 percent of patients with breast cancer appear to have primary tumors that overexpress VEGF compared to surrounding normal tissue. In fairly large, albeit retrospective analyses, this population of patients had a higher rate of relapse. So there's a clear biologic hypothesis and rationale for exploring this strategy of utilizing bevacizumab in the adjuvant setting.

A major issue is whether we have the safety data to bring bevacizumab into this setting. Should we wait until we have the results of E-2100? Should we start looking at pilot approaches in the adjuvant setting now? Should we start planning adjuvant trials? We're certainly considering these questions in the Eastern Cooperative Oncology Group.

— George W Sledge Jr, MD