Anti-Angiogenic Therapy

The importance of angiogenesis in cancer biology has been recognized for decades. However, only recently have investigators begun to recognize the complexity of tumor micro-environment signaling and tumor vasculature. Increased understanding of angiogenesis has led to the identification of a number of angiogenesic stimulators and inhibitors. One of the first stimulating factors identified is the vascular endothelial growth factor (VEGF). At the 2002 San Antonio Breast Cancer Symposium, Kathy Miller and colleagues report on the first Phase III randomized trial in breast cancer evaluating the anti-VEGF monoclonal antibody bevacizumab. The trial compared the oral fluoropyrimidine prodrug capecitabine alone or combined with bevacizumab in heavily pretreated patients with metastatic breast cancer, and found a modest response rate advantage to the combination. Several other Phase II and III clinical trials are ongoing.

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

Protocol IDs: Genentech-AVF2119g, GUMC-00299, MSKCC-01008, UAB-0028, UAB-F001009003
Projected Accrual: 462 patients

Eligibility	**Metastatic breast cancer previously treated with 1-2 chemotherapy regimens for metastatic disease or no prior chemotherapy for metastatic disease if previously treated with an adjuvant anthracycline or taxane regimen and relapsed within 12 months**
ARM 1	**Capecitabine 1,250 mg/m² bid (days 1-14) q3w**
ARM 2	**Capecitabine 1,250 mg/m² bid (days 1-14) q3w + bevacizumab (day 1) q3w**

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

SOURCE: NCI Physician Data Query, January 2003

EFFICACY AND TOXICITY OF CAPECITABINE + BEVICUZIMAB VERSUS CAPECITABINE ALONE

	Capecitabine (n=230)	Capecitabine + bevacizumab (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
Hypertension (grade 3)	0.5%	17.9%
Thromboembolic PE DVT	5.6% 1.4% 2.3%	7.4% 1.3% 6.1%
Bleeding Grade ≥ 3	11.2% 1.4%	28.8% 0.4%
Proteinuria	7.4%	22.3%
Cardiac (Grade 3 or 4)	0.9%	3.1%

DERIVED FROM: Kathy Miller, Presentation, 2002 San Antonio Breast Cancer Symposium

PHASE III RANDOMIZED STUDY OF PACLITAXEL WITH OR WITHOUT BEVACIZUMAB IN PATIENTS WITH LOCALLY RECURRENT OR METASTATIC BREAST CANCER — Open Protocol

Protocol IDs: E-2100, CTSU
Projected Accrual: 316-650 patients

Eligibility	**Locally recurrent disease not amenable to resection with curative intent or metastatic disease radiotherapy**
ARM 1	**Paclitaxel qw + bevacizumab q2w**
ARM 2	**Paclitaxel qw**

In both arms, treatment repeats q4w x 18 in the absence of disease progression or unacceptable toxicity.

Study Contact
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SOURCE: NCI Physician Data Query, January 2003

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

Chair	Protocol IDs	Status	Accrual	Study Arms
Miller	E-2100 CTSU	Open	316-650	Bevacizumab q2w + Paclitaxel qw vs Paclitaxel qw
Low	NCI-01-C-0173 NCI-2722	Open	23	(Bevacizumab + AT + G-CSF q3w) x 7 ➜ Surgery ➜ Bevacizumab q3w x 8
Overmoyer	CWRU-3100 NCI-2722	Open	60	Bevacizumab q2w + T qw vs T qw --- Patients with stable or responsive disease ➜ Surgery ➜ AC x 4
Burstein	DFCI-01013 NCI-2716	Closed	43-56	Bevacizumab q2w + Vinorelbine qw

A = doxorubicin; C = cyclophosphamide; T = docetaxel
SOURCE: NCI Physician Data Query, January 2003

MATHEMATICAL MODELING: RATIONALE FOR THE DELIVERY OF CHEMOTHERAPY AND ANTI-ANGIOGENIC AGENTS

If you give an antivascular agent, you may be decreasing the proliferation index of the endothelial cells just at the time you want to kill those endothelial cells with chemotherapy. By combining chemotherapy directly with an antivascular agent you may obtain absolutely no benefit. You may be inhibiting cell kill and inhibiting regrowth and that balances out exactly. It would be better to give chemotherapy, then give an antivascular agent, have a washout period and then give chemotherapy. That washout period may be a problem, but there are newer classes of agents that you may be able to use where the washout time may be faster and the half-life may be shorter.

— Larry Norton, MD

PHASE III RANDOMIZED TRIAL EVALUATING CAPECITABINE WITH OR WITHOUT BEVACIZUMAB

This is the first randomized Phase III trial to be completed that evaluates anti-angiogenic therapy in patients with metastatic breast cancer. This was a very refractory group of patients. The majority of patients had prior anthracyclines, taxanes, and some other therapy before they entered this trial. They were randomized to capecitabine alone or with bevacizumab given every three weeks as a single IV infusion.

The toxicity data were quite reassuring. There was no difference in common capecitabine toxicities. We saw the expected bevacizumab toxicities, based on our Phase II experience. Hypertension that required intervention was observed in about 20% of patients and10% –20% of patients had mild to moderate proteinuria. Bleeding was slightly increased if you looked at nuisance Grade I and II bleeding, but Grade III bleeding was extremely uncommon. There was a very slight increase in thrombosis — predominantly DVT and line-associated thrombosis — with no increase in serious thrombotic events or pulmonary embolism.

The efficacy data also confirms the activity of this agent. There was a near doubling of response rates. We learned something interesting when we looked at duration of response. Even though the combination increased response rates, most of those additional responses were fairly short-lived, so the proportion of long-term responders was the same in both groups. Not surprisingly, the progression-free survival was the same in both groups.

—Kathy Miller, MD

PHASE III TRIAL OF PACLITAXEL WITH OR WITHOUT BEVACIZUMAB IN PATIENTS WITH NEWLY DIAGNOSED METASTATIC BREAST CANCER

ECOG-2100 moves treatment with bevacizumab earlier into the course of treatment with newly diagnosed patients. We will also collect primary tumor tissue, serum and urine samples for investigation of potential surrogates of response to VEGF-targeted therapies. The other thing we need to figure out is how to select the patients who are most likely to respond to this type of therapy. Right now it is a targeted therapy, but we don't select patients based on the presence of the target because we don't know how to do that. So, this trial tries to take advantage of what we do know about the drug and the patients most likely to benefit while collecting other material that will allow us to select future patients on the basis of molecular factors rather than just disease natural history.

—Kathy Miller, MD

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