Given the well-established role of angiogenesis (or new blood vessel formation) in tumor growth and metastasis, antiangiogenic therapy, a concept first proposed by Dr. Judah Folkman,[1] has become increasingly recognized as a promising new anticancer strategy. As the angiogenic switch in tumors reflects the net balance of a diverse group of endogenous angiogenic promoters and inhibitors, a multitude of agents have been developed to target different factors and pathways. Over 20 antiangiogenic drugs are currently undergoing evaluation in phase I, II, and III trials.

Clinical Trials Referral Resource is designed to serve as a ready reference for oncologists to help identify clinical trials that might be suitable for their patients. We hope it will also enhance accrual to clinical trials by informing practicing oncologists of ongoing protocols. Currently in the United States less than 10% of eligible adult patients are entered into clinical trials. The result is a delay in answering important therapeutic and scientific questions and disseminating therapeutic advances to the general oncology community.

It should be emphasized that including a specific trial does not imply that it is more important than another trial. Among the criteria for selection are that the trial is addressing an important question and is not expected to close in the immediate future (less than 1 year), and that initial staging or laboratory tests required for patient eligibility are widely practiced and available. Information on other protocols can be accessed via Physician’s Data Query (PDQ).*

We emphasize that this is an attempt to encourage referral of patients to these trials. We are specifically not soliciting additional members for the cooperative groups, nor are we suggesting how practicing oncologists should be treating patients who are not in a study.

This month’s installment of Clinical Trials Referral Resource is devoted to clinical trials of the anti-vascular endothelial growth factor monoclonal antibody bevacizumab.

For patient entry information, see the individual trials.

Of known proangiogenic factors, vascular endothelial growth factor (VEGF; also known as the vascular permeability factor) is one of the most potent and specific, and has been identified as a crucial regulator of both normal and pathologic angiogenesis. VEGF is a secreted, heparin-binding protein that exists in multiple isoforms due to alternative splicing. The action of VEGF is mainly mediated through binding of the circulating VEGF peptides to receptor tyrosine kinases on endothelial cells, VEGFR-1 (Flt-1), and VEGFR-2 (KDR/Flk-1). The biological effects of VEGF include endothelial cell mitogenesis and migration, induction of proteinases leading to remodeling of the extracellular matrix, increased vascular permeability, maintenance of survival for newly formed blood vessels, and possibly suppression of dendritic cell maturation.[2]

Overexpression of VEGF has been demonstrated in most human cancers examined to date. In breast cancer, increased levels of VEGF, as measured in the circulation or in tumor tissues, correlated with
an increase in microvessel density and advanced disease stages, and in some cases, independently predicted reduced relapse-free and overall survival.[3,4] A similar correlation was also implicated in a variety of other solid tumors.[5] More recently, the importance of endothelial cells and angiogenesis has also been suggested in hematologic malignancies, such as aggressive lymphoma, myelogenous leukemia, multiple myeloma, myelodysplasia, and others.

The apparent significance of VEGF in cancer pathogenesis supports the rationale for VEGF-targeting therapeutics. Anti-VEGF agents currently in clinical trials include monoclonal antibodies targeting the VEGF ligand (eg, bevacizumab) and inhibitors directed at the receptors (eg, SU5416).

Bevacizumab (rhuMAb VEGF, Genentech, Inc) is a recombinant humanized anti-VEGF monoclonal antibody (MAb) that recognizes all biologically active isoforms of VEGF and blocks their binding to the VEGF receptors.[6,7] Bevacizumab is composed of the antigen-binding complementarity-determining regions from a murine anti-VEGF MAb (A.4.6.1) and the human immunoglobin G1 framework. Anti-VEGF MAbs have shown potent growth inhibition in vivo in a variety of human cancer xenograft[7,8] and metastasis models,[9] including rhabdomyosarcoma, glioblastoma, breast, lung, colon cancer, and others. Such a growth inhibitory effect was accompanied by a reduction in vascular permeability, decrease in tumor vessel density, and in some cases, complete suppression of angiogenesis.[11,12] Furthermore, the combination of anti-VEGF MAb and chemotherapeutic agents, such as doxorubicin[10] and cisplatin (Platinol), resulted in enhanced antitumor activity compared to either agent alone.

Several clinical trials have evaluated bevacizumab at different doses and schedules.[13,14] Pharmacokinetics appeared to be linear at doses above 1 mg/kg, with a half-life of ~15 days. Recommended doses for further studies are 5 or 10 mg every 2 weeks or 15 mg every 3 weeks. Evidence of single-agent activity has been demonstrated in a phase II study in patients with previously treated metastatic breast cancer,[14] where objective tumor responses, including one complete response, were documented.

The combination of bevacizumab and chemotherapy was also evaluated. In a phase II trial of bevacizumab and fluorouracil (5-FU) plus leucovorin, 104 patients with untreated metastatic colorectal cancer were randomized to either chemotherapy alone, or in combination with two dose levels of bevacizumab.[15,16] Although the study was not designed and powered to compare efficacy, the combination arms suggested a trend toward a higher response rate and longer time to tumor progression. Genentech is currently sponsoring a phase III trial comparing irinotecan (CPT-11, Camptosar), 5-FU, and leucovorin with or without bevacizumab as first-line therapy for metastatic colorectal cancer.

The combination of bevacizumab with carboplatin (Paraplatin) plus paclitaxel (Taxol) was also tested for safety and feasibility in a small randomized phase II trial in patients with advanced non-small-cell lung cancer (NSCLC).[17,18] There appeared to be an advantage for the higher dose of bevacizumab (15 mg/kg every 2 weeks), but the results were not statistically significant. In this trial, several major hemorrhagic events were reported in the bevacizumab arm, as indicated below.[19]

A variety of side effects have been reported in the clinical studies of bevacizumab. Most significant were hemorrhagic events in the NSCLC study of the bevacizumab and carboplatin/paclitaxel combination, in which 6 of the 66 patients developed life-threatening pulmonary hemorrhage (4 of which were fatal)[19]; most patients had tumors of squamous cell histology or central location. Life-threatening hemorrhage was not observed in other bevacizumab trials, although bleeding graded as serious has been reported. Hypertension attributable to bevacizumab was common (about 20%) but in most cases, was mild or controllable with medication. Proteinuria of varying severity has been reported. In the study of bevacizumab with 5-FU and leucovorin, there also appeared to be an increase in thromboembolic events in the combination arm compared to chemotherapy alone. Other events less clinically significant included epistaxis, headache, diarrhea, fever, and rash.

The mechanisms and risk factors for bevacizumab-related toxicities remain unknown. At present, all ongoing clinical trials have implemented specific exclusion criteria and early stopping rules to minimize risk to patients, with special attention to bleeding, thrombosis, and cardiovascular events.
In view of the critical role of VEGF in tumor pathogenesis and the preliminary efficacy data of bevacizumab, the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) has established an agreement to develop bevacizumab in collaboration with Genentech, Inc. The CTEP is currently sponsoring a number of clinical trials of bevacizumab, ranging from phase I to phase III.

The general goals of these trials include: (1) assessing the activity of bevacizumab in various solid tumors and hematologic malignancies, (2) evaluating the safety and efficacy of combining bevacizumab with conventional chemotherapy and radiation, or with other targeted and biological agents, (3) exploring the surrogate and predictive markers of anti-VEGF therapy, and (4) understanding the mechanism of action and treatment failure. A list of currently open or approved NCI-sponsored trials is provided below. Information about these trials can be obtained from the contact listed for each trial or from Helen Chen, MD, at the NCI’s CTEP (chenh@ctep.nci.nih.gov), (301) 496-8798.

**Head and Neck Cancer**

**Title:** A Phase I Study of Bevacizumab (Recombinant Humanized Monoclonal Antibody to Vascular Endothelial Growth Factor) in addition to Fluorouracil and Hydroxyurea as Initial Chemotherapy with Concomitant Radiotherapy (B-FHX) for Poor Prognosis Head and Neck Cancer  
**Protocol Number:** 2630  
**Participating Institution:** University of Chicago  
**Protocol Status:** In review  
**Contact:** Everett E. Vokes, MD, (773) 702-9306

**Non-Small-Cell Lung Cancer**

**Title:** Phase II/III Randomized Study of Paclitaxel and Carboplatin With or Without Bevacizumab in Patients With Advanced, Metastatic, or Recurrent Non-Squamous Cell Non-Small Cell Lung Cancer  
**Protocol Number:** E-4599 (Intergroup)  
**Participating Group:** Eastern Cooperative Oncology Group  
**Protocol Status:** Active  
**Contact:** Robert L. Comis, Eastern Cooperative Oncology Group, (215) 789-3645 (CTSU Investigators: see footnote)*  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** A Phase II Study of Neoadjuvant rhuMAb VEGF (Bevacizumab) in Combination with Paclitaxel and Carboplatin in Surgically Resectable Non-Small-Cell Lung Cancer  
**Protocol Number:** 2655  
**Participating Institution:** Ohio State University Hospital  
**Protocol Status:** In review  
**Contact:** Gregory Otterson, MD, (614) 293-6786

**Mesothelioma**

**Title:** A Double Blind, Placebo Controlled Randomized Phase II Trial of Gemcitabine and Cisplatin with or without the VEGF Inhibitor Bevacizumab (NSC #704865) in Patients with Malignant Mesothelioma  
**Protocol Number:** 2710 (in review)  
**Participating Institutions:** University of Chicago, Lutheran General Hospital, Evanston Hospital, University of Illinois, Weiss Memorial Hospital, Decatur Memorial Hospital, Oncology-Hematology Associates, Fort Wayne Medical Oncology/Hematology Incorporated, Michiana Hematology Oncology PC, Central Illinois Hematology Oncology Center  
**Protocol Status:** In review  
**Contact:** Hedy Lee Kindler, MD, (773) 702-0360
Breast Cancer

**Title:** Phase II Pilot Study of Bevacizumab, Docetaxel, Doxorubicin, and Filgrastim (G-CSF) in Patients With Previously Untreated Stage IIIB or IV Inflammatory Breast Cancer  
**Protocol Number:** 2772  
**Participating Institution:** National Cancer Institute Medicine Branch  
**Protocol Status:** Active  
**Contact:** Sandra M. Swain, Medicine Branch, (301) 496-4916  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** A Randomized Phase II Study of Bevacizumab in Combination with Docetaxel in Locally Advanced Breast Cancer  
**Protocol Number:** 2722  
**Participating Institution:** Case Western Reserve University  
**Protocol Status:** In review  
**Contact:** Beth A. Overmayer, MD, (216) 844-8573

**Title:** Phase II Study of Concurrent Bevacizumab and Vinorelbine in Patients With Stage IV Breast Cancer  
**Protocol Number:** NCI-2716  
**Participating Institutions:** Dana-Farber Cancer Center, Massachusetts General Hospital, Beth Israel Deaconess Medical Center  
**Protocol Status:** Active  
**Contact:** Harold J. Burstein, MD, (617) 632-5340  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase II Study of Bevacizumab in Combination with Docetaxel in Patients with Advanced and metastatic Breast Cancer  
**Protocol Number:** 2715  
**Participating Institution:** University of Colorado  
**Protocol Status:** In review  
**Contact:** Pablo J. Cagnoni, MD, (303) 372-9000

**Title:** A Randomized Phase III Trial of Paclitaxel vs Paclitaxel plus Bevacizumab (rhuMAB VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer  
**Protocol Number:** E2100  
**Participating Group:** Eastern Cooperative Oncology Group  
**Protocol Status:** In review  
**Contact:** Jean MacDonald, (617) 632-3610

Pancreatic Cancer

**Title:** A Phase II Trial of Bevacizumab (NSC #704865) plus Gemcitabine in Patients with Advanced Pancreatic Cancer  
**Protocol Number:** 2675  
**Participating Institutions:** University of Chicago, Loyola University Medical Center, Weiss Memorial Hospital, Decatur Memorial Hospital, Oncology-Hematology Associates, Ingalls Memorial Hospital, La Grange Memorial Hospital, La Grange Treatment Pavillion, Fort Wayne Medical Oncology/Hematology Incorporated, Michiana Hematology Oncology PC, Lakeland Medical Center Saint Joseph  
**Protocol Status:** In review  
**Contact:** Hedy Lee Kindler, MD, (773) 702-0360

Colorectal Cancer

**Title:** Phase II Study of Fluorouracil, Leucovorin Calcium, Irinotecan, and Bevacizumab (Monoclonal
Antibody Anti-VEGF) in Patients With Previously Untreated Advanced Colorectal Cancer

**Protocol Number:** E-2200  
**Participating Group:** Eastern Cooperative Oncology Group  
**Protocol Status:** Active  
**Contact:** Bruce J. Giiantonio, Eastern Cooperative Oncology Group, (215) 662-8756; for a complete listing of study contacts, click here  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase III Trial of Bevacizumab, Oxaliplatin, Fluorouracil, and Leucovorin vs Oxaliplatin, Fluorouracil, and Leucovorin vs Bevacizumab Alone in Previously Treated Patients with Advanced Colorectal Cancer  
**Protocol Number:** E3200 (Intergroup, in review)  
**Participating Group:** Eastern Cooperative Oncology Group  
**Protocol Status:** In review  
**Contact:** Jean MacDonald, (617) 632-3610, (CTSU Investigators: see footnote)*

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**Renal Cancer**

**Title:** Phase II Randomized Study of Monoclonal Antibody VEGF in Patients With Unresectable Advanced Renal Cell Cancer  
**Protocol Number:** T98-0035  
**Participating Institution:** National Cancer Institute Surgery Branch  
**Protocol Status:** Active  
**Contact:** James Chung-Yin Yang, Surgery Branch, (301) 496-1574  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Prostate Cancer**

**Title:** A Randomized Phase II Trial of Neoadjuvant Bevacizumab, Docetaxel, and Emcyt vs Docetaxel Plus Emcyt in Patients with High-Grade Prostate Cancer Eligible for Radical Prostatectomy  
**Protocol Number:** 2619  
**Participating Institution:** University of California at Los Angeles  
**Protocol Status:** In review  
**Contact:** Fairooz F. Kabbinavar, MD, (310) 206-0868

**Ovarian and Peritoneal Cancer**

**Title:** Phase II Study of Bevacizumab in Patients With Persistent or Recurrent Ovarian Epithelial or Primary Peritoneal Cancer  
**Protocol Number:** GOG-0170-D  
**Participating Group/Institutions:** Gynecologic Oncology Group, University of California Medical Center at Irvine, Orange County Regional Cancer Center  
**Protocol Status:** Active  
**Contact:** Robert C. Park, Gynecologic Oncology Group, (215) 854-0770  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Cervical Cancer**

**Title:** A Phase II Trial of Bevacizum (rhuMAB VEGF) (NSC #704865, IND #7921) in the Treatment of Advanced and Recurrent Squamous Cell Carcinoma of the Cervix  
**Protocol Number:** GOG-0227-C  
**Participating Group:** Gynecologic Oncology Group  
**Protocol Status:** In review  
**Contact:** Bradley J. Monk, MD, (714) 456-6570
Melanoma

Title: A Phase II Study of Bevacizumab and Interferon-Alfa-2b in Metastatic Malignant Melanoma
Protocol Number: 2669
Participating Institution: Ohio State University Hospital
Protocol Status: In review
Contact: William E. Carson, MD, (614) 293-6306

Hematological Malignances Multiple Myeloma

Title: Phase II Randomized Study of Bevacizumab With or Without Thalidomide in Patients With Relapsed or Refractory Multiple Myeloma
Protocol Number: 2712
Participating Institutions: City of Hope Medical Center, University of Southern California, Stanford University, University of California at Davis
Protocol Status: Active
Contact: George Somlo, Beckman Research Institute, City of Hope, (626) 359-8111
Beckman Research Institute, City of Hope
Latest Information: http://cancernet.nci.nih.gov/

Non-Hodgkin’s Lymphoma (NHL)

Title: Phase II Study of Bevacizumab in Patients With Relapsed Aggressive Non-Hodgkin's Lymphoma
Protocol Number: S0108
Participating Group: Southwest Oncology Group
Protocol Status: Active
Contact: Alison T. Stopeck, Southwest Oncology Group, (520) 626-2816; for a complete listing of study contacts, click here
Latest Information: http://cancernet.nci.nih.gov/

Chronic Myelogenous Leukemia (CML)

Title: A Phase II Study of Bevacizumab (rhuMAB VEGF, NSC #704865), Idarubicin, and Cytarabine in Patients with Chronic Myeloid Leukemia in Blast Phase
Protocol Number: 2431
Participating Institution: M. D. Anderson Cancer Center
Protocol Status: In review
Contact: Jorge E. Cortes, MD, (713) 794-5783

Acute Myelogenous Leukemia (AML)

Title: Phase II Study of Bevacizumab, Cytarabine, and Mitoxantrone in Patients With Poor-Risk Hematologic Malignancies
Protocol Number: NCI-2490
Participating Institutions: University of Maryland Cancer Center, Johns Hopkins University
Protocol Status: Active
Contact: Judith E. Karp, Marlene & Stewart Greenebaum Cancer Center, University of Maryland, (410) 328-7394
Latest Information: http://cancernet.nci.nih.gov/

Myelodysplastic Syndrome

Title: Phase I/II Study of Bevacizumab in Patients With Myelodysplastic Syndrome
Current Clinical Trials of the Anti-VEGF Monoclonal Antibody Bevacizumab
Published on Physicians Practice (http://www.physicianspractice.com)

Protocol Number: NCI-2771
Participating Institution: Stanford University, M. D. Anderson Cancer Center, Arizona Cancer Center
Protocol Status: Active
Contact: Peter L. Greenberg, Stanford University Medical Center, (650) 725-8355
Latest Information: http://cancernet.nci.nih.gov/

Genentech-Sponsored Trials

Title: Phase III Randomized Study of Bevacizumab With Capecitabine Versus Capecitabine Alone in Women With Previously Treated Metastatic Breast Cancer
Protocol Number: AVF2119g
Participating Institutions: Multiple institutions in the United States
Protocol Status: Active
Contact: Ginny Langmuir, Genentech Inc., (650) 225-4985; for a complete listing of study contacts, click here
Latest Information: http://cancernet.nci.nih.gov/

Title: Phase III Randomized Study of Bevacizumab With Fluorouracil and Leucovorin Calcium With or Without Irinotecan in Patients With Metastatic Colorectal Cancer
Protocol Number: AVF2107g
Participating Institutions: Multiple institutions in the United States
Protocol Status: Active
Contact: Beth Drena, Genentech Inc., (650) 225-6762; for a complete listing of study contacts, click here
Latest Information: http://cancernet.nci.nih.gov/

Title: Phase II Randomized Study of Fluorouracil and Leucovorin Calcium With or Without Bevacizumab in Patients With Previously Untreated Metastatic Colorectal Cancer Who Are Not Optimal Candidates for First-Line Irinotecan
Protocol Number: AVF2192g
Participating Institutions: Multiple institutions in the United States
Protocol Status: Active
Contact: Spencer Guthrie, Genentech Inc., (650) 225-7647; for a complete listing of study contacts, click here
Latest Information: http://cancernet.nci.nih.gov/

References:


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