VEGF-C, VEGF-D, VEGF-E, VEGF-F, and PlGF. VEGF-A primarily binds to two high affinity receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR), the latter being the major transmitter of vascular endothelial cell mitogenic signals of VEGF-A. Additionally, neuropilin-1 has been identified as a receptor for heparin-binding VEGF-A isoforms, and may play a role in vascular development.

In addition to being an angiogenic factor in angiogenesis and vasculogenesis, VEGF, as a pleiotropic growth factor, exhibits multiple biological effects in other physiological processes, such as endothelial cell survival, vessel permeability and vasodilation, monocyte chemotaxis and calcium influx. Ferrara and Davis-Smyth (1997), *supra*. Moreover, studies have reported mitogenic effects of VEGF on a few non-endothelial cell types, such as retinal pigment epithelial cells, pancreatic duct cells and Schwann cells. Guerrin et al. *J. Cell Physiol.* 164:385-394 (1995); Oberg-Welsh et al. *Mol. Cell. Endocrinol.* 126:125-132 (1997); Sondell et al. *J. Neurosci.* 19:5731-5740 (1999).

The recognition of VEGF as a primary regulator of angiogenesis in pathological conditions has led to numerous attempts to block VEGF activities in conditions that involve pathological angiogenesis. VEGF expression is upregulated in a majority of malignancies and the overexpression of VEGF correlates with a more advanced stage or with a poorer prognosis in many solid tumors. Therefore, molecules that inhibit VEGF signaling pathways have been used for the treatment of relatively advanced solid tumors in which pathological angiogenesis is noted.

Since cancer is still one of the most deadly threats, additional cancer treatments for patients are needed. Specifically, treatments for patients with MBC are needed to improve control of disease to prevent symptoms, while minimizing toxicity. The invention addresses these and other needs, as will be apparent upon review of the following disclosure.

SUMMARY

In one aspect, there is provided the use of an anti-VEGF antibody in the manufacture of a medicament for treating locally recurrent or metastatic breast cancer in a subject, the medicament comprises at least one chemotherapeutic agent and an anti-VEGF antibody, wherein said subject has not received any chemotherapy for locally recurrent or metastatic breast cancer, and/or has not received prior adjuvant chemotherapy in recurrence less than or equal to 12 months since last dose; and wherein the chemotherapeutic agent is FEC: 5-fluorouracil, epirubicin, and cyclophosphamide, or FAC: 5-fluorouracil, doxorubicin and cyclophosphamide, or AC: doxorubicin and cyclophosphamide, or EC: Epirubicin and cyclophosphamide; and wherein the treatment regimen effectively extends the progression free survival of the subject.

The ~~invention~~disclosure concerns uses of anti-VEGF antibody for effectively treating breast cancer patients for previously untreated metastic breast cancer. In particular, the ~~invention~~disclosure provides data from a randomized phase III clinical trial of bevacizumab (AVASTIN®) in combination with chemotherapy regimes in subjects with previously untreated metastic breast cancer in human subjects. Such chemotherapy regimes include taxane therapy (e.g., docetaxel or paclitaxel protein-bound particles (e.g., Abraxane®)), anthracycline therapy (e.g., doxorubicin, epirubicin or combinations thereof) or capecitabine therapy. In some embodiments, the treatment is used as first line therapy for locally recurrent or previously

thereof. Two or more chemotherapeutic agents can be used (e.g., in a cocktail) to be administered in combination with administration of the anti-VEGF antibody.

Clinical benefits of the any of the methods, uses and compositions provided herein according to the ~~invention~~disclosure can be measured by, for example, duration of progression free survival (PFS), time to treatment failure, objective response rate and duration of response.

Accordingly, the ~~invention~~disclosure features a method of instructing a human subject with, e.g., breast, cancer by providing instructions to receive treatment with an anti-VEGF antibody so as to increase progression free survival of the subject, to decrease the subject's risk of cancer recurrence or to increase the subject's likelihood of survival. In some embodiments the method further comprises providing instructions to receive treatment with at least one chemotherapeutic agent. The treatment with the anti-VEGF antibody may be concurrent with or sequential to the treatment with the chemotherapeutic agent. In certain embodiments the subject is treated as instructed by the method of instructing.

The ~~invention~~disclosure also provides a promotional method, comprising promoting the administration of an anti-VEGF antibody for treatment of, e.g., breast, cancer in a human subject. In some embodiments the method further comprises promoting the administration of at least one chemotherapeutic agent. Administration of the anti-VEGF antibody may be concurrent with or sequential to administration of the chemotherapeutic agent. Promotion may be conducted by any means available. In some embodiments the promotion is by a package insert accompanying a commercial formulation of the anti-VEGF antibody. The promotion may also be by a package insert accompanying a commercial formulation of the chemotherapeutic agent. Promotion may be by written or oral communication to a physician or health care provider. In some embodiments the promotion is by a package insert where the package inset provides instructions to receive therapy with anti-VEGF antibody. In some embodiments the promotion is followed by the treatment of the subject with the anti-VEGF antibody with or without the chemotherapeutic agent.

The ~~invention~~disclosure provides a business method, comprising marketing an anti-VEGF antibody for treatment of, e.g., breast, cancer in a human subject so as to increase progression free survival, or decrease the subject's likelihood of cancer recurrence or increase the subject's likelihood of survival. In some embodiments the method further comprises marketing a chemotherapeutic agent for use in combination with the anti-VEGF antibody. In some embodiments the marketing is followed by treatment of the subject with the anti-VEGF antibody with or without the chemotherapeutic agent.

Also provided is a business method, comprising marketing a chemotherapeutic agent in combination with an anti-VEGF antibody for treatment of, e.g., breast, cancer in a human subject so as to increase progression free survival, or decrease the subject's likelihood of cancer recurrence or increase the subject's likelihood of survival. In some embodiments, the marketing is followed by treatment of the subject with the combination of the chemotherapeutic agent and the anti-VEGF antibody.

In any of the methods, uses and compositions provided herein, the anti-VEGF antibody may be substituted with a VEGF specific antagonist, e.g., a VEGF receptor molecule or chimeric VEGF receptor molecule as described herein. In certain embodiments of the methods, uses and compositions provided herein, the anti-VEGF antibody is bevacizumab. The anti-VEGF antibody, or antigen-binding fragment thereof, can be a monoclonal antibody, a chimeric antibody, a fully human antibody, or a humanized antibody. Exemplary antibodies useful in the methods of the ~~invention~~disclosure include bevacizumab (AVASTIN®), a G6 antibody, a B20 antibody, and fragments thereof. In certain embodiments, the anti-VEGF antibody has a heavy chain variable region comprising the following amino acid sequence:

EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID No. 1)

and a light chain variable region comprising the following amino acid sequence:

DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR (SEQ ID No. 2).

The antibody, or antigen-binding fragment thereof, can also be an antibody that lacks an Fc portion, an $F(ab')_2$, an Fab, or an Fv structure.

In one embodiment of the methods, uses and compositions provided herein, the treatment is a combination of a VEGF-specific antagonist, e.g., anti-VEGF antibody, and at least one chemotherapeutic agent. In other embodiments of the methods, uses and compositions provided herein, the VEGF-specific antagonist is a monotherapy.

Each of any of the methods, uses and compositions provided herein may be practiced in relation to the treatment of cancers including, but not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include breast

cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, gastric cancer, melanoma, and various types of head and neck cancer. In some embodiments of the methods of the ~~invention~~disclosure the subject has metastatic breast cancer. In some embodiments of the methods, uses and compositions provided herein the subject has previously untreated metastatic breast cancer. In some embodiments the subject has HER2-negative metastic breast cancer.

Each of the above aspects can further include monitoring the subject for recurrence of the cancer. Monitoring can be accomplished, for example, by evaluating progression free survival (PFS) or overall survival (OS) or objective response rate (ORR). In one embodiment, the PFS or the OS or the ORR is evaluated after initiation of treatment.

Depending on the type and severity of the disease, preferred dosages for the anti-VEGF antibody, e.g., bevacizumab, are described herein and can range from about 1μg/kg to about 50 mg/kg, most preferably from about 5 mg/kg to about 15 mg/kg, including but not limited to 5 mg/kg, 7.5 mg/kg, 10 mg/kg or 15 mg/kg. The frequency of administration will vary depending on the type and severity of the disease. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until the cancer is treated or the desired therapeutic effect is achieved, as measured by the methods described herein or known in the art. In one example, the anti-VEGF antibody is administered once every week, every two weeks, or every three weeks, at a dose range from about 5 mg/kg to about 15 mg/kg, including but not limited to 5 mg/kg, 7.5 mg/kg, 10 mg/kg or 15 mg/kg. However, other dosage regimens may be useful. The progress of the therapy of the ~~invention~~disclosure is easily monitored by conventional techniques and assays.

In additional embodiments of each of the above aspects, the VEGF-specific antagonist, e.g., anti-VEGF antibody is administered locally or systemically (e.g., orally or intravenously). In other embodiments, one aspect of the treatment is with the VEGF-specific antagonist in a monotherapy or a monotherapy for the duration of the VEGF-specific antagonist treatment period, e.g., in extended treatment phase or maintenance therapy, as assessed by the clinician or described herein.

In other embodiments of the methods, uses and compositions provided herein, treatment, use or composition with the VEGF-specific antagonist is in combination with an additional anti-cancer therapy, including but not limited to, surgery, radiation therapy, chemotherapy, differentiating therapy, biotherapy, immune therapy, an angiogenesis inhibitor, a cytotoxic agent and/or an anti-proliferative compound. Treatment, use and composition with the VEGF-specific antagonist can also include any combination of the above types of therapeutic regimens. In some embodiments, the chemotherapeutic agent and the VEGF-specific antagonist are administered concurrently.

In the embodiments of the methods, uses and compositions provided herein which include an additional anti-cancer therapy, the subject can be further treated with the additional anti-cancer therapy before, during (e.g., simultaneously), or after administration of the VEGF-specific antagonist. In one embodiment, the VEGF-specific antagonist, administered either alone or with an anti-cancer therapy, can be administered as maintenance therapy.

Other features and advantages of the ~~invention~~disclosure will be apparent from the following Detailed Description, the drawings, and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the study design for the metastatic breast cancer trial using bevacizumab (BV) or placebo (PL) with various chemotherapies.

Figure 2 depicts progression free survival (PFS) curves for capecitabine arm of the trial. INV (investigator) is PFS assessed by investigator and IRC is PFS assessed by independent review committee (IRC), where placebo is PL and bevacizumab is BV.

Figure 3 depicts PFS curves for taxane/anthracycline arm of the trial. INV is PFS assessed by investigator and IRC is PFS assessed by independent review committee (IRC), where placebo is PL and bevacizumab is BV.

Figure 4 depicts a subgroup analyses of PFS in the capecitabine and taxane/anthracycline groups of the trial.

Figure 5 depicts the objective response rate for capecitabine (Cape) and taxane/anthracycline (T/Antra) groups.

Figure 6 depicts a subgroup analysis of PFS for taxane/anthracycline (T/Anthra) cohorts.