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). VEGF expression is upregulated in a majority of malignancies and the overexpression of VEGF often correlates with a more advanced stage or with a poorer prognosis in many solid tumors.

Since ovarian cancer is still one of the most deadly threats, additional cancer treatments for patients are needed. 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 bevacizumab in the manufacture of a medicament for treating a patient diagnosed with stage III or IV ovarian cancer, wherein the bevacizumab is to be administered every three weeks at 15mg/kg for five cycles , starting at cycle 2, and carboplatin at a dose of an area under the curve of 6 and paclitaxel at a dose of 175 mg/m$^2$ are to be administered every three weeks for six cycles, starting on cycle 1; wherein a maintenance dose of said bevacizumab at 15 mg/kg every three weeks is to be administered for cycles 7 through 22; and wherein the treatment regimen effectively extends the progression free survival of the patient.

Provided is the use of anti-VEGF antagonists for treating ovarian cancer. For example, uses of anti-VEGF antibodies for effectively treating women with newly diagnosed, previously untreated ovarian, fallopian tube or primary peritoneal cancer or platinum sensitive recurrent (or previously treated) ovary, primary, peritoneal, or fallopian tube carcinoma are provided. Data is provided from a randomized phase III clinical trial of bevacizumab (AVASTIN®) in combination with chemotherapy regimes in subjects (e.g., women) with newly diagnosed, previously untreated stage III (sub optimally and macroscopic optimally debulked) and IV epithelial ovarian, primary peritoneal or fallopian tube cancer (Example 1). Data is also provided from a randomized phase III clinical trial of bevacizumab (AVASTIN®) in combination with chemotherapy regimes in subjects (e.g., women) with newly diagnosed, high risk stage I and IIa (Grade 3 or clear cell carcinoma only) and stage IIb - IV epithelial ovarian, fallopian tube or primary peritoneal cancer, who have undergone initial surgery and who would not be considered for cytoreductive surgery prior to disease progression (Example

2). Data is also provided from a placebo-controlled, randomized, multicenter Phase III study evaluating the efficacy and safety of bevacizumab (15 mg/kg, Day 1, every 21 days), administered in combination with carboplatin (area under the curve [AUC] 4, Day 1, every 21 days) with gemcitabine (1000 mg/m$^2$, Day 1 and Day 8, every 21 days) in women with platinum sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma (Example 3). Such chemotherapy regimes include taxane therapy (e.g., paclitaxel or docetaxel), platinum based chemotherapy (e.g., carboplatin) or gemcitabine, and combinations thereof. The success of the trials show that providing anti-VEGF antibody (e.g., bevacizumab) when combined with chemotherapy and continued as maintenance therapy provides statistically significant and clinically meaningful benefits to ovarian cancer patients.

The results obtained in clinical studies of the use of bevacizumab in both concurrent and maintenance treatment in human subjects with previously untreated and recurrent ovarian cancer show that the efficacy, as evaluated by progression free survival (PFS) was positive especially when compared to PFS data for treatment with chemotherapeutic agents alone. Subjects in the clinical trials who received bevacizumab in concurrent treatment in combination with taxane therapy (e.g., paclitaxel or docetaxel), and platinum based chemotherapy (e.g., carboplatin) or platinum based chemotherapy (e.g., carboplatin) and gemcitabine and maintenance therapy with bevacizumab had an increase in progression free survival compared to subjects treated with taxane therapy (e.g., paclitaxel or docetaxel), and platinum based chemotherapy (e.g., carboplatin) alone or platinum based chemotherapy (e.g., carboplatin) and gemcitabine alone.

Accordingly, the disclosure~~invention~~ provides a method of treating a patient diagnosed with previously untreated or recurrent ovarian cancer, comprising subjecting the patient to a treatment regimen combining at least one chemotherapy with the administration of an effective amount of an anti-VEGF antibody, and then administering the anti-VEGF antibody for maintenance therapy wherein with said treatment the progression free survival of the patient is increased. The treatment regimen combining the chemotherapy with the administration of the anti-VEGF and then the administration of anti-VEGF maintenance therapy effectively extends the progression free survival (PFS) of the patient.

In certain embodiments, the PFS is extended about 1 month, 1.2 months, 2 months, 2.9 months, 3 months, 3.8 months, 4 months, 6 months, 7 months, 8 months, 9 months, 1 year, about 2 years, about 3 years, etc, compared to a control. In one embodiment, the PFS is extended about 2.9 months to 3.8 months (e.g., with the treatment regimen combining the chemotherapy with the administration of the anti-VEGF and then the administration of anti-VEGF maintenance therapy) compared to a control. In one embodiment, the PFS is extended at least about 3.8 months (e.g., with the treatment regimen combining the chemotherapy with the administration of the anti-VEGF and then the administration of anti-VEGF maintenance therapy) compared to a control. In another embodiment, the PFS is extended about 2.3 months (e.g., with the treatment regimen combining the chemotherapy with the administration of the anti-VEGF and then the administration of anti-VEGF maintenance therapy) compared to a control. In one embodiment, the PFS is extended about 6 months (e.g., with the treatment regimen combining the chemotherapy with the administration of the anti-VEGF and then the administration of anti-VEGF maintenance therapy) compared to a control.

Any chemotherapeutic agent exhibiting anticancer activity can be used according to the present disclosure~~invention~~. In certain embodiments, the chemotherapeutic agent is selected from the group consisting of alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitor, interferons, platinum cordination complexes, taxanes anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, gemcitabine and gonadotropin-releasing hormone analog. In certain embodiments, the chemotherapeutic agent is for example, taxane, paclitaxel, docetaxel, paclitaxel protein-bound particles (e.g., Abraxane®), gemcitabine, platinum analogs, carboplatin, or combinations thereof. Two or more chemotherapeutic agents can be used in a cocktail to be administered in combination with administration of the anti-VEGF antibody, e.g., taxane and platinum analogs or gemcitabine and platinum analogs. In one embodiment, it is carboplatin and paclitaxel. In one embodiment, it is carboplatin and docetaxel. In another embodiment, it is gemcitabine and carboplatin.

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

Kits are also provided. In one aspect, there is provided a kit for treating previously untreated stage III or IV ovarian cancer in a human patient comprising a package comprising an anti-VEGF antibody composition and instructions for using the anti-VEGF antibody composition in combination with paclitaxel and carboplatin followed by anti-VEGF maintenance therapy, wherein the instructions recite that the progression free survival for patients receiving paclitaxel, carboplatin and anti-VEGF antibody is 18.3 months with a hazard ratio of 0.79; wherein the anti-VEGF antibody is bevacizumab; wherein the bevacizumab is to be administered every three weeks at 15mg/kg for five cycles , starting at cycle 2, and carboplatin at a dose of an area under the curve of 6 and paclitaxel at a dose of 175 mg/m$^2$ are to be administered every three weeks for six cycles, starting on cycle 1; wherein a maintenance dose of said bevacizumab at 15 mg/kg every three weeks is to be administered for cycles 7 through 22. In one embodiment, a kit is provided for treating previously

untreated ovarian cancer in a human patient comprising a package comprising an anti-VEGF antibody composition and instructions for using the anti-VEGF antibody composition in combination with taxane therapy and carboplatin followed by anti-VEGF maintenance therapy, wherein the instructions recite that the progression free survival for patients receiving taxane therapy and carboplatin therapy and bevacizumab is 14.1 months with a hazard ratio of 0.717 (p-value <0.0001). In another embodiment, a kit is provided for treating previously untreated ovarian cancer in a human patient comprising a package comprising an anti-VEGF antibody composition and instructions for using the anti-VEGF antibody composition in combination with paclitaxel and carboplatin followed by anti-VEGF maintenance therapy, wherein the instructions recite that the progression free survival for patients receiving paclitaxel, carboplatin and anti-VEGF antibody is 18.3 months with a hazard ratio of 0.79. In certain embodiments, a kit comprises an anti-VEGF antibody that 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). In certain embodiments, the anti-VEGF antibody is bevacizumab in the kit. In certain embodiments, the kit is for a patient that has stage III or IV ovarian cancer.

Accordingly, the disclosure~~invention~~ features a method of instructing a human subject with, e.g., ovarian, 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. In some embodiments, the method further comprises providing instructions to receive treatment with at least two chemotherapeutic agents. In certain embodiments, the treatment with the anti-VEGF antibody is both concurrent and sequential to the treatment with the chemotherapeutic agent. In certain embodiments the subject is treated as instructed by the method of instructing.

The disclosure~~invention~~ also provides a promotional method, comprising promoting the administration of an anti-VEGF antibody for treatment of, e.g., ovarian, cancer in a human subject. In some embodiments the method further comprises promoting the administration of at least one chemotherapeutic agent. In certain embodiments of the disclosure~~invention~~, the administration of the anti-VEGF antibody is both concurrent and sequential to administration of the chemotherapeutic agent(s). 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(s). 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 concurrent therapy with an anti-VEGF antibody and at least one chemotherapy agent(s) and maintenance therapy with an anti-VEGF antibody. In some

embodiments the promotion is followed by the treatment of the subject with an anti-VEGF antibody with one or more chemotherapeutic agent(s) followed by maintenance therapy with an anti-VEGF antibody.

The disclosure~~invention~~ provides a business method, comprising marketing an anti-VEGF antibody for treatment of, e.g., ovarian, cancer in a human subject in combination with at least one chemotherapy agent followed by anti-VEGF maintenance therapy 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 anti-VEGF antibody with the chemotherapeutic agent(s) followed by anti-VEGF maintenance therapy. In some embodiments the method further comprises marketing two or more chemotherapeutic agents for use in combination with the anti-VEGF antibody followed by anti-VEGF maintenance therapy. In some embodiments the marketing is followed by treatment of the subject with the anti-VEGF antibody with the chemotherapeutic agents followed by anti-VEGF maintenance therapy.

Also provided is a business method, comprising marketing a chemotherapeutic agent in combination with an anti-VEGF antibody followed by anti-VEGF maintenance therapy for treatment of, e.g., ovarian, 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 followed by the anti-VEGF maintenance therapy. Also provided is a business method, comprising marketing two or more chemotherapeutic agents in combination with an anti-VEGF antibody followed by anti-VEGF maintenance therapy for treatment of, e.g., ovarian, 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 agents and the anti-VEGF antibody followed by anti-VEGF maintenance therapy.

In each of the methods of the disclosure~~invention~~ 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 below. In certain embodiments, 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 disclosure~~invention~~ 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, the treatment is a combination of a VEGF-specific antagonist, e.g., anti-VEGF antibody, and at least one chemotherapeutic agent followed by VEGF antagonist maintenance therapy. In one embodiment, the treatment is a combination of a VEGF-specific antagonist, e.g., anti-VEGF antibody, and two or more chemotherapeutic agents followed by VEGF antagonist maintenance therapy.

Each of the methods or uses of the disclosure~~invention~~ 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 ovarian cancer, ovarian primary peritoneal cancer, ovarian fallopian tube 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, liver cancer, bladder cancer, hepatoma, breast cancer, 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, the subject has previously untreated ovarian cancer. In some embodiment, the subject has newly diagnosed previously untreated ovarian cancer. In some embodiments, the subject has newly diagnosed, previously untreated, stage III (sub optimally

and macroscopic optimally debulked) and IV epithelial ovarian primary peritoneal or fallopian tube cancer. In some embodiments, the subject has platinum sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma.

Each of the above embodimentaspects 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 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 of the disclosureinvention 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 disclosureinvention is easily monitored by conventional techniques and assays. In certain embodiments of the disclosureinvention, anti-VEGF therapy is provided as maintenance therapy. In further embodiments, anti-VEGF therapy is provided for at least 14 months (including concurrent anti-VEGF therapy with chemotherapy and anti-VEGF maintenance therapy). In other embodiments, anti-VEGF therapy is provided for at least 12 months (including concurrent anti-VEGF therapy with chemotherapy and anti-VEGF maintenance therapy).

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 certain embodiments, the anti-VEGF maintenance therapy is given for at least cycles 7 through 22. In other embodiments, the anti-VEGF maintenance therapy is given for at least cycles 7 through 18.

In other embodiments, treatment 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 an anti-proliferative compound. Treatment 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 followed by anti-VEGF maintenance therapy. In some embodiments, two or more chemotherapeutic agents and the VEGF-specific antagonist are administered concurrently followed by anti-VEGF maintenance therapy.

In the embodiments 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 disclosure~~invention~~ 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 ovarian cancer trial described in Example 1.

**Figure 2** depicts a diagram of the study design for the ovarian cancer trial using bevacizumab (BEV) or placebo with various chemotherapies.

**Figure 3** depicts select adverse events from the trial depicted in Figure 2.

**Figure 4** depicts select adverse events by treatment phase from the trial depicted in Figure 2.

**Figure 5** depicts Investigator-assessed progression free survival (PFS) of Arm I, Arm II and Arm III of the trial depicted in Figure 2.

**Figure 6** depicts PFS values for Arm I and Arm III of the trial depicted in Figure 2 and the ramifications of using CA-125 marker as determinant of progression.

**Figure 7** depicts a subgroup analyses of patients in Arm III verses Arm I of the trial depicted in Figure 2.

**Figure 8** depicts the study design for the ovarian cancer trial described in Example 2.

**Figure 9** depicts a summary of the progression free survival (PFS) analysis of the trial depicted in Figure 8. "CP" corresponds to Arm A in Figure 8. "CPB7.5+" corresponds to Arm B in Figure 8.

**Figure 10** depicts a graph of the PFS results from the trial depicted in Figure 8. "CP" corresponds to Arm A in Figure 8. "CPB7.5+" corresponds to Arm B in Figure 8.

**Figure 11** depicts the study design for the ovarian cancer trial described in Example 3.

4. A promotional method, comprising promoting administration of an anti-VEGF antibody, wherein the anti-VEGF antibody is bevacizumab; wherein the bevacizumab is to be administered every three weeks at 15mg/kg for five cycles , starting at cycle 2, and carboplatin at a dose of an area under the curve of 6 and paclitaxel at a dose of 175 mg/m$^2$ are to be administered every three weeks for six cycles, starting on cycle 1; wherein a maintenance dose of said bevacizumab at 15 mg/kg every three weeks is to be administered for cycles 7 through 22; for treatment of stage III or IV ovarian cancer in a human subject so as to increase progression free survival of the subject.

5. The method of claim 4, wherein the promotion is selected from the group consisting of: (a) a promotion by a package insert, wherein the package insert provides instructions to receive cancer treatment with bevacizumab,

(b) a promotion by a package insert accompanying a commercial formulation of bevacizumab,

(c) a promotion by a package insert accompanying a commercial formulation of the paclitaxel and carboplatin,

(d) a promotion by written communication to a physician or health care provider, and

(e) a promotion by oral communication to a physician or health care provider.

6. The method of claim 4, wherein the promotion is to be followed by the treatment of the subject with the bevacizumab, , paclitaxel and carboplatin, followed by bevacizumab maintenance therapy.

7. A business method, comprising marketing an anti-VEGF antibody therapy concurrent with chemotherapy followed by anti-VEGF maintenance therapy for treatment of stage III or IV ovarian cancer in a human subject so as to increase progression free survival of the subject, wherein the anti-VEGF antibody is bevacizumab; wherein the bevacizumab is to be administered every three weeks at 15mg/kg for five cycles , starting at cycle 2, and carboplatin at a dose of an area under the curve of 6 and paclitaxel at a dose of 175 $mg/m^2$ are to be administered every three weeks for six cycles, starting on cycle 1; wherein a maintenance dose of said bevacizumab at 15 mg/kg every three weeks is to be administered for cycles 7 through 22.

8. The method of claim 7, wherein the marketing is to be followed by treatment of the subject with the bevacizumab concurrent with chemotherapy followed by bevacizumab maintenance therapy.

49. A kit for treating previously untreated stage III or IV ovarian cancer in a human patient comprising a package comprising an anti-VEGF antibody composition and instructions for using the anti-VEGF antibody composition in combination with paclitaxel and carboplatin followed by anti-VEGF maintenance therapy, wherein the instructions recite that the progression free survival for patients receiving paclitaxel, carboplatin and anti-VEGF antibody is 18.3 months with a hazard ratio of 0.79; wherein the anti-VEGF antibody is bevacizumab; wherein the bevacizumab is to be administered every three weeks at 15mg/kg for five cycles , starting at cycle 2, and carboplatin at a dose of an area under the curve of 6 and paclitaxel at a dose of 175 mg/m$^2$ are to be administered every three weeks for six cycles, starting on cycle 1; wherein a maintenance dose of said bevacizumab at 15 mg/kg every three weeks is to be administered for cycles 7 through 22.