$CD11b^+Gr1^+$ cells produce several angiogenic factors, including Bv8, a secreted protein previously characterized as a mitogen for specific endothelial cell type, as a growth factor for hematopoietic progenitors (LeCouter *et al.*, *Proc Natl Acad Sci USA* 100, 2685-2690 (2003); LeCouter *et al.*, *Proc Natl Acad Sci USA* 101, 16813-16818 (2004)), and as a neuromodulator (Cheng *et al.*, *Nature* 417, 405-410 (2002); Matsumoto *et al., Proc Natl Acad Sci USA* 103:4140–4145 (2006)). Analysis of several xenografts, as well as of a transgenic cancer model (RIP-Tag), suggested that Bv8 promotes tumor angiogenesis through increased peripheral mobilization of myeloid cells and local stimulation of angiogenesis (Shojaei *et al., Nature* 450:825-831 (2007); Shojaei *et al.*, *Proc Natl Acad Sci USA* 105:2640-2645 (2008)). It has been reported that granulocyte colony stimulating factor (G-CSF) as a strong inducer of Bv8 expression, both *in vitro* and *in vivo* (Shojaei *et al., Proc Natl Acad Sci USA* 106(16):6742-7 (2009)). Physiologically, G-CSF has an important role in mobilization of hematopoietic stem cells, progenitors, and mature cells, particularly neutrophils, into the blood circulation (Rapoport *et al.*, *Blood Rev* 6:43–57 (1992); Lieschke *et al.*, *Blood* 84:1737–1746 (1994)). G-CSF is also necessary for differentiation of progenitors to cells of granulocytic lineage, such as neutrophils, eosinophils and basophils. Although a few reports have suggested that G-CSF administration enhances tumor angiogenesis and growth (Natori *et. al.*, *Biochem Biophys Res Commun* 297:1058–1061 (2002); Okazaki, T. et al., *Int Immunol* 18, 1-9 (2006)), the evidence implicating this factor in tumorigenesis is far from conclusive.

Metastasis is a complex series of steps in which cancer cells leave the original tumor site and migrate to other parts of the body via the bloodstream or the lymphatic system. Metastatic tumors are very common in the late stages of cancer. Metastasis is a major cause of death from solid tumors. Unfortunately, the treatment options currently available are rarely able to cure metastatic cancer.

Thus, there is a need to discover and understand how angiogenesis and tumor metastatic progression can be effectively inhibited, prevented and treated. The present invention addresses these and other needs, as will be apparent upon review of the following disclosure.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~disclosure is based, at least in part, on the discovery that G-CSF and Bv8 are involved in angiogenesis and tumor metastasis.

In one aspect, there is provided the use of an antagonistic anti-G-CSF antibody or an antigen-binding fragment thereof in the manufacture of a medicament for inhibiting or reducing tumor metastasis.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting or reducing tumor metastasis comprising administering to a subject an effective amount of a G-CSF antagonist. In certain

embodiments, the method further comprises administering to the subject an effective amount of Bv8 antagonist. In certain embodiments, the G-CSF antagonist inhibits or reduces the spread of a primary tumor to a pre-metastatic organ of the subject. In certain embodiments, reducing tumor metastasis comprises reducing size or number of lung metastases. In certain embodiments, inhibiting or reducing tumor metastasis comprises reducing one or more expression levels of the following molecules: G-CSF, Bv8, PKR1, MMP-9, S100A8 or S100A9. In certain embodiments, inhibiting or reducing tumor metastasis comprises reducing expression levels of G-CSF and PKR1. In certain embodiments, inhibiting or reducing tumor metastasis comprises reducing expression levels of MMP-9, S100A8 and S100A9. In certain embodiments, inhibiting or reducing tumor metastasis comprises reducing expression levels of Bv8, MMP-9, S100A8 and S100A9. In certain embodiments, inhibiting or reducing tumor metastasis comprises reducing expression levels of G-CSF, Bv8 and PKR1. In certain embodiments, the expression levels are mRNA expression levels. In certain embodiments, the expression levels are protein expression levels. In certain embodiments, expression levels of one or more of these molecules are reduced in a pre-metastatic organ of the subject. In certain embodiments, the pre-metastatic organ is lung. In certain embodiments, the pre-metastatic organ is liver.

In certain embodiments, the methods further comprise administering to the subject an effective amount of VEGF antagonist. In certain embodiments, the subject has been previously treated with VEGF antagonist. In certain embodiments, the VEGF antagonist is an anti-VEGF antibody or a fragment thereof. In certain embodiments, the anti-VEGF antibody is bevacizumab or a fragment or variant thereof. In certain embodiments, the methods further comprise administering to the subject an effective amount of a chemotherapeutic agent.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of reducing expression level of G-CSF, Bv8, PKR1, MMP-9, S100A8 or S100A9 in a pre-metastatic organ comprising administering to the subject an effective amount of a G-CSF antagonist and/or Bv8 antagonist. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of reducing expression level of one or more of the following molecules, G-CSF, Bv8, PKR1, MMP-9, S100A8 or S100A9, in a pre-metastatic organ comprising administering to the subject an effective amount of a G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, expression levels of PKR1, MMP-9, S100A8 and/or S100A9 are reduced in the pre-metastatic organ of the subject when G-CSF antagonist is administered to the subject. In certain embodiments, expression levels of PKR1, MMP-9, S100A8 and/or S100A9 are reduced in the pre-metastatic organ of the subject when Bv8

antagonist is administered to the subject. In certain embodiments, expression levels of Bv8, MMP-9, S100A8 and/or S100A9 are reduced in the pre-metastatic organ of the subject when G-CSF antagonist is administered to the subject. In certain embodiments, expression levels of Bv8, MMP-9, S100A8 and/or S100A9 are reduced in the pre-metastatic organ of the subject when Bv8 antagonist is administered to the subject. In certain embodiments, expression levels of MMP-9, S100A8 and S100A9 are reduced in the pre-metastatic organ of the subject when G-CSF antagonist is administered to the subject. In certain embodiments, expression levels of MMP-9, S100A8 and S100A9 are reduced in the pre-metastatic organ of the subject when Bv8 antagonist is administered to the subject. In certain embodiments, expression levels of G-CSF and PKR1 are reduced in the pre-metastatic organ of the subject when G-CSF antagonist is administered to the subject. In certain embodiments, expression levels of G-CSF, PKR1 and MMP-9 are reduced in the pre-metastatic organ of the subject when G-CSF antagonist is administered to the subject.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting migration of metastatic tumor cells to a pre-metastatic organ comprising administering to the subject an effective amount of a G-CSF antagonist or Bv8 antagonist. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting migration of neutrophils to a pre-metastatic organ comprising administering to the subject an effective amount of a G-CSF antagonist or Bv8 antagonist. In certain embodiments, the methods comprise administering to the subject an effective amount of the G-CSF antagonist and an effective amount of the Bv8 antagonist.

In certain embodiments, the pre-metastatic organ of the subject is lung, liver, brain, bone or lymph node. In certain embodiments, the pre-metastatic organ of the subject is lung or liver. In certain embodiments, the pre-metastatic organ of the subject is lung.

In certain embodiments, the G-CSF antagonist is an anti-G-CSF antibody. In certain embodiments, the anti-G-CSF antibody is a monoclonal antibody. In certain embodiments, the anti-G-CSF antibody is a humanized antibody. In certain embodiments, the anti-G-CSF antibody is a human antibody.

In certain embodiments, the Bv8 antagonist is an anti-Bv8 antibody. In certain embodiments, the Bv8 antagonist is an anti-PKR1 antibody. In certain embodiments, the anti-Bv8 antibody or anti-PKR1 antibody is a monoclonal antibody. In certain embodiments, the anti-Bv8 antibody or anti-PKR1 antibody is a humanized antibody. In certain embodiments, the anti-Bv8 antibody or anti-PKR1 antibody is a human antibody.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of predicting whether a tumor in a

subject will respond effectively to treatment with a G-CSF antagonist and/or Bv8 antagonist comprising determining whether a sample from the subject comprises a cell that expresses Bv8, PKR1 and/or G-CSF at a level greater than the expression level in a reference sample, wherein detection of said cell indicates that the subject has the tumor that will respond effectively to treatment with said G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, the detection of a cell that expresses Bv8, PKR1 and G-CSF at levels greater than the expression levels in a reference sample indicates that the subject has the tumor cells that will respond effectively to treatment with said G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, the mRNA expression levels of Bv8, PKR1 and/or G-CSF are measured. In certain embodiments, the protein expression levels of Bv8, PKR1 and/or G-CSF are measured. In certain embodiments, the tumor is metastatic tumor.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of predicting whether a tumor in a subject will respond effectively to treatment with a G-CSF antagonist and/or Bv8 antagonist comprising determining whether a sample from the subject comprises a functional human counterpart of CD11b+Gr1+ cell that expresses Bv8 at a level greater than the expression level in a reference sample, wherein detection of said functional human counterpart of CD11b+Gr1+ cell indicates that the subject has the tumor that will respond effectively to treatment with said G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, the mRNA expression level of Bv8 is measured. In certain embodiments, the protein expression level of Bv8, is measured. In certain embodiments, the human counterpart cells are human immature myeloid cells. In certain embodiments, the human counterpart cells are human myeloid derived suppressor cells. In certain embodiments, the human counterpart cells are precursors of human neutrophils, monocytes or macrophages. In certain embodiments, the human counterpart cells are human neutrophils, monocytes or macrophages. In certain embodiments, the tumor is metastatic tumor.

In yet another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of predicting whether a tumor in a subject will respond effectively to treatment with a G-CSF antagonist and/or Bv8 antagonist comprising determining whether a sample from the subject has increased number or frequency of functional human counterpart of CD11b+Gr1+ cells compared to a reference sample, wherein the increased number or frequency of functional human counterpart of CD11b+Gr1+ cells indicates that the subject has the tumor that will respond effectively to treatment with said G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, the human counterpart cells are human immature myeloid cells. In certain embodiments, the human counterpart cells are

human myeloid derived suppressor cells. In certain embodiments, the human counterpart cells are precursors of human neutrophils, monocytes or macrophages. In certain embodiments, the human counterpart cells are neutrophils, monocytes or macrophages. In certain embodiments, the tumor is metastatic tumor.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of treating a tumor in a subject with a G-CSF antagonist and/or Bv8 antagonist comprising (a) determining whether a sample from the subject comprises a cell that expresses Bv8, PKR1 and/or G-CSF at a level greater than the expression level in a reference sample, and (b) if the sample comprises a cell that expresses Bv8, PKR1 and/or G-CSF at a level greater than the expression level in the reference sample, administering to the subject an effective amount of said G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, the cell is a functional human counterpart of CD11b+Gr1+ cell. In certain embodiments, the human counterpart cells are human immature myeloid cells. In certain embodiments, the human counterpart cells are human myeloid derived suppressor cells. In certain embodiments, the human counterpart cells are precursors of human neutrophils, monocytes or macrophages. In certain embodiments, the human counterpart cell is neutrophils, monocytes or macrophages. In certain embodiments, the cell is metastatic tumor cell. In certain embodiments, the cells are from a pre-metastatic organ of the subject. In certain embodiments, if the sample comprises a cell that expresses Bv8, PKR1 and G-CSF at levels greater than the expression levels in the reference sample, then an effective amount of said G-CSF antagonist and/or Bv8 antagonist is administered to the subject.

In certain embodiments, the mRNA expression levels of Bv8, PKR1 and/or G-CSF are measured. In certain embodiments, the protein expression levels of Bv8, PKR1 and/or G-CSF are measured.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of treating a tumor in a subject with a G-CSF antagonist and/or Bv8 antagonist comprising (a) determining whether a sample from the subject has increased number or frequency of functional human counterpart of CD11b+Gr1+ cells compared to a reference sample, and (b) if the sample has the increased number or frequency of functional human counterpart of CD11b+Gr1+ cells compared to the reference sample, administering to the subject an effective amount of said G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, the human counterpart cells are human immature myeloid cells. In certain embodiments, the human counterpart cells are human myeloid derived suppressor cells. In certain embodiments, the human counterpart cells are precursors of human neutrophils, monocytes or macrophages. In certain embodiments, the human counterpart cells

are neutrophils, monocytes or macrophages. In certain embodiments, the tumor is metastatic tumor.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of treating tumor, comprising (a) administering to a tumor-bearing subject an effective amount of a G-CSF antagonist, and (b) monitoring the efficacy of said treatment by determining the number or frequency of functional human counterpart of CD11b+Gr1+ cells in a sample obtained from the subject after the treatment, relative to the number or frequency of functional human counterpart of CD11b+Gr1+ cells in a sample obtained from the subject before the treatment, wherein a reduced number or frequency of functional human counterpart of CD11b+Gr1+ cells in the sample obtained from the subject after the treatment indicates that the treatment is effective. In certain embodiments, the human counterpart cells are human immature myeloid cells. In certain embodiments, the human counterpart cells are human myeloid derived suppressor cells. In certain embodiments, the human counterpart cells are precursors of human neutrophils, monocytes or macrophages. In certain embodiments, the human counterpart cells are neutrophils, monocytes or macrophages. In certain embodiments, the tumor is metastatic tumor.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of treating tumor, comprising (a) administering to a tumor-bearing subject an effective amount of a G-CSF antagonist and/or Bv8 antagonist, and (b) monitoring the efficacy of said treatment by determining the expression level of Bv8, MMP-9, S100A8 or S100A9 in a sample obtained from the subject after the treatment, relative to the expression level of Bv8, MMP-9, S100A8 or S100A9 in a sample obtained from the subject before the treatment, wherein a reduced expression level of Bv8, MMP-9, S100A8 or S100A9 in the sample obtained from the subject after the treatment indicates that the treatment is effective.

In certain embodiments, expression levels of at least two of the following four molecules, Bv8, MMP-9, S100A8 and S100A9, are reduced in the sample obtained from the subject after the treatment compared to the sample obtained from the subject before the treatment. In certain embodiments, expression levels of at least three of the following four molecules, Bv8, MMP-9, S100A8 and S100A9, are reduced in the sample obtained from the subject after the treatment compared to the sample obtained from the subject before the treatment. In certain embodiments, the mRNA expression levels of Bv8, MMP-9, S100A8 and/or S100A9 are measured. In certain embodiments, the protein expression levels of Bv8, MMP-9, S100A8 and/or S100A9 are measured. In certain embodiments, the tumor is

metastasizing to pre-metastatic tissues or pre-metastatic organs elsewhere in the body. In certain embodiments, the sample from the subject is a tissue, plasma, serum, or any combinations thereof. In certain embodiments, the samples used in these methods are from a pre-metastatic or metastatic organ. In certain embodiments, the pre-metastatic or metastatic organ is lung, liver, brain, bone, lymph node or ovary. In certain embodiments, the samples are from a pre-metastatic or metastatic tissue. In certain embodiments, the pre-metastatic or metastatic tissue is from subject's lung, liver, brain, ovary, lymph node, bone or bone marrow. In certain embodiments, the sample is a tissue sample from a pre-metastatic organ. In certain embodiments, if the sample is from pre-metastatic organ or pre-metastatic tissue, the sample does not contain any tumor cells. In certain embodiments, the sample is primary tumor tissue.

In certain embodiments, the mRNA expression level of a gene is measured using qRT-PCR or qPCR. In certain embodiments, the mRNA expression level is measured using microarrary. In certain embodiments, the mRNA expression level is measured using ISH (in situ hybridization). In certain embodiments, the protein expression level of a gene is measured using IHC assay.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting mobilization of functional human counterpart of CD11b+Gr1+ cells from the bone marrow to a pre-metastatic or metastatic organ comprising administering to a subject an effective amount of a G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, the human counterpart cells are human immature myeloid cells. In certain embodiments, the human counterpart cells are human myeloid derived suppressor cells. In certain embodiments, the human counterpart cells are precursors of human neutrophils, monocytes or macrophages. In certain embodiments, the human counterpart cell is neutrophils, monocytes or macrophages.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of treating tumor in a subject relapsed from or refractory to anti-cancer therapy comprising administering to a subject an effective amount of a G-CSF antagonist. In certain embodiments, the anti-cancer therapy comprises a VEGF antagonist. In certain embodiments, the VEGF antagonist is an anti-VEGF antibody or fragment thereof. In certain embodiments, the anti-VEGF antibody is bevacizumab or a fragment or variant thereof.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of treating a benign, pre-cancerous, or non-metastatic cancer in a subject, comprising administering to the subject an effective amount of a G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, administering of the G-CSF antagonist and/or Bv8 antagonist prevents the benign, pre-cancerous, or non-metastatic

cancer from becoming an invasive or metastatic cancer. In certain embodiments, the benign, pre-cancerous, or non-metastatic cancer is a stage 0, stage I, or stage II cancer. In certain embodiments, administering of the G-CSF antagonist and/or Bv8 antagonist prevents the benign, pre-cancerous or non-metastatic cancer from progressing to a stage III or stage IV cancer. In certain embodiments, administering of the G-CSF antagonist and/or Bv8 antagonist reduces tumor size.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of treating a subject with operable cancer comprising administering to the subject an effective amount of a G-CSF antagonist and/or Bv8 antagonist and performing surgery whereby the cancer is resected. In certain embodiments, the G-CSF antagonist and/or Bv8 antagonist is administered to the subject prior to surgery. In certain embodiments, the methods further comprise the step of administering to the subject an effective amount of the G-CSF antagonist and/or Bv8 antagonist after surgery to prevent recurrence of the cancer. In certain embodiments, administering of the G-CSF antagonist and/or Bv8 antagonist prevents proliferation of micrometastases.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of neoadjuvant therapy in a subject with operable cancer comprising administering to the subject a G-CSF antagonist and/or Bv8 antagonist.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of preventing recurrence of cancer in a subject, comprising administering to the subject a G-CSF antagonist and/or Bv8 antagonist, wherein said administering prevents cancer recurrence in the subject. In yet another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of reducing the likelihood of cancer recurrence in a subject, comprising administering to the subject a G-CSF antagonist and/or Bv8 antagonist, wherein said administering reduces the likelihood of cancer recurrence in the subject. In certain embodiments, the administering of the G-CSF antagonist and/or Bv8 antagonist prevents or reduces the likelihood of reoccurrence of a clinically detectable tumor, or metastasis thereof. In certain embodiments, the subject has had definitive surgery prior to the administering the G-CSF antagonist and/or Bv8 antagonist.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of preventing the regrowth of a tumor in a subject comprising the steps of removing the tumor and thereafter administering to the subject a G-CSF antagonist and/or Bv8 antagonist. In yet another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of preventing the recurrence of cancer in a subject having a tumor comprising the steps of removing the tumor and thereafter administering to the subject a G-CSF antagonist and/or Bv8 antagonist. In certain embodiments, the methods further comprise a period of time

between removal of the tumor and administering the G-CSF antagonist and/or Bv8 antagonist, wherein the period of time is sufficient for the surgical incision to be fully healed or to reduce the risk of wound dehiscence.

In certain embodiments, the G-CSF antagonist administered is an anti-G-CSF antibody or a fragment thereof. In certain embodiments, the Bv8 antagonist administered is an anti-Bv8 antibody or a fragment thereof. In certain embodiments, the Bv8 antagonist administered is an anti-PKR1 antibody or a fragment thereof.

In certain embodiments, the antagonists and antibodies of the present ~~invention~~disclosure are administered sequentially. In certain embodiments, the antagonists and antibodies of the present ~~invention~~disclosure are administered concurrently.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting lung metastasis, liver metastasis, brain metastasis, ovary metastasis, lymph node metastasis and/or bone metastasis comprising administered to a subject an effective amount of an anti-G-CSF antibody and/or anti-Bv8 antibody. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting lung metastasis comprising administered to a subject an effective amount of an anti-G-CSF antibody, wherein the anti-G-CSF antibody inhibits tumor from metastasizing to a pre-metastatic lung. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting lung metastasis comprising administered to a subject an effective amount of an anti-Bv8 antibody, wherein the anti-Bv8 antibody inhibits tumor from metastasizing to a pre-metastatic lung. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting lung metastasis comprising administered to a subject an effective amount of an anti-PKR1 antibody, wherein the anti-PKR1 antibody inhibits tumor from metastasizing to a pre-metastatic lung. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting lung metastasis comprising administered to a subject an effective amount of an anti-G-CSF antibody and an effective amount of an anti-Bv8 antibody. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting lung metastasis comprising administered to a subject an effective amount of an anti-G-CSF antibody and an effective amount of an anti-PKR1 antibody. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting lung metastasis comprising administered to a subject an effective amount of an anti-Bv8 antibody and an effective amount of an anti-PKR1 antibody.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting liver metastasis comprising administered to a subject an effective amount of an anti-G-CSF antibody, wherein the anti-G-CSF antibody inhibits tumor from metastasizing to a pre-metastatic liver. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting liver metastasis comprising administered to

a subject an effective amount of an anti-Bv8 antibody, wherein the anti-Bv8 antibody inhibits tumor from metastasizing to a pre-metastatic liver. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of inhibiting liver metastasis comprising administered to a subject an effective amount of an anti-PKR1 antibody, wherein the anti-PKR1 antibody inhibits tumor from metastasizing to a pre-metastatic liver.

In certain embodiments, the antibodies or antibody fragments can be chimeric, humanized or human.

In certain embodiments, the methods of the present ~~invention~~disclosure further comprise administering to the subject an effective amount of a VEGF antagonist. In certain embodiments, the subject has a tumor previously treated with a VEGF antagonist. In certain embodiments, the subject is relapsed from or refractory to a VEGF antagonist. In certain embodiments, the VEGF antagonist is an anti-VEGF antibody or a fragment thereof. In certain embodiments, the anti-VEGF antibody is bevacizumab or a fragment or variant thereof. In certain embodiments, the methods of the present ~~invention~~disclosure further comprise administering to the subject an effective amount of a chemotherapeutic agent. In certain embodiments, the subject being treated is subjected to chemotherapy and/or radiation therapy, where the chemotherapy may, for example, comprise the administration of a cytotoxic agent. In certain embodiments, the additional treatment is a treatment known as "standard of care" for the treatment of the particular tumor targeted. In certain embodiments, the G-CSF antagonist is administered in combination with a different anti-tumor agent and/or treatment regiment, such as chemotherapy and/or radiation therapy. In certain embodiments, the Bv8 antagonist is administered in combination with a different anti-tumor agent and/or treatment regiment, such as chemotherapy and/or radiation therapy. In certain embodiments, the methods of the present ~~invention~~disclosure further comprise administration of an additional inhibitor of angiogenesis, such as, for example, an antibody to an angiogenic factor.

In certain embodiments, the subject is mammal. In certain embodiments, the subject is human. In certain embodiments, the subject is diagnosed with cancer. In certain embodiments, the tumor is cancer. In certain embodiments, the metastatic tumor is cancer. In certain embodiments, the cancer is colon cancer, lung cancer, breast cancer, renal cell cancer, ovarian cancer, prostate cancer, bladder cancer, melanoma or glioblastoma.

Any embodiment described above or any combination thereof applies to any and all methods of the ~~inventions~~disclosures described herein.