

Yang et al., 2008, Clin. Cancer Res., 14:5893-5899; Hurwitz et al., 2004, N. Engl. J. Med., 350:2335-2342). However, as in previous studies of angiogenesis inhibitors, some of these phase-III studies have shown that a portion of patients experience incomplete response to the addition of bevacizumab to their chemotherapeutic regimens.

Accordingly, there is a need for methods of identifying those patients that are likely to respond or have an improved response to not only angiogenesis inhibitors (e.g., bevacizumab) alone, but also combination therapies comprising angiogenesis inhibitors (e.g., bevacizumab).

## SUMMARY

Disclosed is a method of treating a patient with a cancer, the method including administering to the patient a therapeutically effective amount of a VEGF antagonist, wherein the patient's cancer has been determined to express CD31 and/or tumor VEGFA at a level more than the median level for CD31 and/or tumor VEGFA expression, respectively, in the cancer type. In one aspect, there is provided use of a VEGF antagonist in the manufacture of a medicament for treating a patient with a gynecologic cancer, wherein a tumor tissue sample obtained from the patient has been determined to express CD31 and VEGFA at a level more than the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer. Disclosed is a VEGF antagonist for use in a method of treating a patient with a cancer, wherein the patient's cancer has been determined to express CD31 and/or tumor VEGFA at a level more than the median level for CD31 and/or tumor VEGFA expression, respectively, in the cancer type, and the method comprises administering to the patient a therapeutically effective amount of the VEGF antagonist. In another aspect, there is provided a VEGF antagonist for use in treating a gynecologic cancer in a patient, wherein a tumor tissue sample obtained from the patient has been determined to express CD31 and VEGFA at a level more than the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer.

In another aspect, there is provided a method of identifying a patient suffering from a gynecologic cancer who may benefit from administration of a VEGF antagonist, the method including: a) determining the expression level of CD31 and VEGFA in a tumor tissue sample that has been obtained from the patient, wherein expression of CD31 and VEGFA at a level more than the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer indicates that the patient may benefit from administration of a VEGF antagonist, and optionally b) wherein the VEGF antagonist is to be administered to the patient.

In another aspect, there is provided a method of predicting responsiveness of a patient to administration of a VEGF antagonist for treatment of a gynecologic cancer, the method including: a) determining the expression level of CD31 and VEGFA in a tumor tissue sample that has been obtained from the patient, wherein expression of CD31 and VEGFA at a level more than the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer indicates that the patient is more likely to be responsive to the administration of the VEGF antagonist, and

liposomal doxorubicin. In other embodiments, the chemotherapy regimen includes the administration of capecitabine and paclitaxel; or capecitabine and docetaxel. In yet other embodiments, the chemotherapy regimen includes the administration of temozolomide and optionally radiotherapy. In a further embodiment, the chemotherapy regimen includes the administration of fluoropyrimidine, irinotecan, cisplatin, fluoropyrimidine and oxaliplatin; fluoropyrimidine and irinotecan; fluoropyrimidine, leucovorin, and oxaliplatin; or irinotecan, fluoropyrimidine, and leucovorin. In yet a further embodiment, the chemotherapy regimen includes the administration of paclitaxel and topotecan; or paclitaxel and cisplatin. In a final embodiment, the chemotherapy regimen includes the administration of interferon-alpha2a.

In another aspect, there is provided a method for the prognosis of a patient suffering from a gynecologic cancer, the method including: a) determining the expression level of CD31 and VEGFA in a tumor tissue sample that has been obtained from the patient, b) comparing the expression level of CD31 and VEGFA to the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer, and c) determining a prognosis for the patient, wherein a poor prognosis is determined when expression of CD31 and VEGFA in the tumor tissue sample obtained from the patient is at a level more than the median level for CD31 and VEGFA expression, respectively, in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

In certain embodiments, the method further includes the step of identifying the patient as likely to benefit from administration of a VEGF antagonist when the patient is determined to have a poor prognosis of survival. In yet another embodiment, the method further includes the step of administering a VEGF antagonist in a therapeutically effective amount to the patient, if the patient is determined to have a poor prognosis. In some embodiments, the VEGF antagonist is an anti-VEGF antibody. In preferred embodiments, the anti-VEGF antibody is bevacizumab.

In one embodiment, the method is carried out prior to administering an anti-cancer agent in order to provide a pre-administration prognosis of survival. In a second embodiment, the survival is progression free survival or overall survival.

Disclosed is a method of treating a patient with a cancer, the method including administering to the patient a therapeutically effective amount of a therapeutic agent other than a VEGF antagonist, wherein the patient's cancer has been determined to express CD31 and/or tumor VEGFA at a level less than the median level for CD31 and/or tumor VEGFA expression, respectively, in the cancer type. Disclosed is use of a therapeutic agent other than a VEGF antagonist in the manufacture of a medicament for treating a cancer in a patient, wherein the patient's cancer has been determined to express CD31 and/or tumor VEGFA at a level less than the median level for CD31 and/or tumor VEGFA expression, respectively, in the cancer type. Disclosed is a therapeutic agent other than a VEGF antagonist for use in a method of treating a patient with a cancer, wherein the patient's cancer has been determined to express CD31 and/or tumor VEGFA at a level less than the median level for CD31 and/or tumor VEGFA expression, respectively, in the cancer type, and the method comprises administering to the

patient a therapeutically effective amount of the therapeutic agent other than a VEGF antagonist. Disclosed is a therapeutic agent other than a VEGF antagonist for use in treating a cancer in a patient, wherein the patient's cancer has been determined to express CD31 and/or tumor VEGFA at a level less than the median level for CD31 and/or tumor VEGFA expression, respectively, in the cancer type.

In one embodiment, the patient's cancer has been determined to express CD31 at a level that is less than the median level for CD31 expression in the cancer type. In another embodiment, the patient's cancer has been determined to express CD31 at a level that is less than the 25<sup>th</sup> percentile for CD31 expression in the cancer type.

In another embodiment, the patient's cancer has been determined to express tumor VEGFA at a level that is less than the median level for tumor VEGFA expression in the cancer type. In another embodiment, the patient's cancer has been determined to express tumor VEGFA at a level that is less than the 25<sup>th</sup> percentile for tumor VEGFA expression in the cancer type.

In particular embodiments of the present disclosures, the cancer is selected from the group consisting of colorectal cancer, breast cancer, non-small cell lung cancer (NSCLC), kidney cancer (renal cell carcinoma), or brain cancer (glioblastoma). In other particular embodiments of the present disclosures, the cancer is a gynecologic cancer selected from the group consisting of ovarian cancer, peritoneal cancer, fallopian tube cancer, cervical cancer, endometrial cancer, vaginal cancer, and vulvar cancer. In preferred embodiments, the gynecologic cancer is ovarian cancer. In yet another embodiment of the present disclosures, the cancer is platinum-resistant, platinum-sensitive, advanced, refractory, or recurrent.

In a further embodiment, the level of CD31 expression detected in the sample of the patient is used to determine the density of CD31 microvascular structures (CD31 MVD) in the cancer of the patient, and optionally wherein CD31 MVD of the patient's sample is compared to the median level of CD31 MVD in the cancer type. In some particular embodiments, CD31 and/or tumor VEGFA expression is detected by an immunohistochemical (IHC) method.

In some preferred embodiments, the VEGF antagonist is an anti-VEGF antibody. In particular preferred embodiments, the anti-VEGF antibody is bevacizumab.

### BRIEF DESCRIPTION OF THE DRAWINGS

**FIG. 1** is a schematic showing a phase III trial design for assessing the effects of adding bevacizumab to a carboplatin-paclitaxel chemotherapy regimen for the treatment of stage III/IV ovarian cancer.

**FIG. 2** is a graph showing the distribution of CD31 expression in a sample patient population.

**FIG. 3** is a table showing the results of a statistical analysis and a Forest plot of

## CLAIMS

1. Use of a VEGF antagonist in the manufacture of a medicament for treating a patient with a gynecologic cancer, wherein a tumor tissue sample obtained from the patient has been determined to express CD31 and VEGFA at a level more than the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer.

2. The use of claim 1, wherein the tumor tissue sample obtained from the patient has been determined to express CD31 at a level that is more than the 75<sup>th</sup> percentile for CD31 expression in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

3. The use of claim 1, wherein the tumor tissue sample obtained from the patient has been determined to express tumor VEGFA at a level that is more than the 75<sup>th</sup> percentile for VEGFA expression in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

4. The use of claim 1, wherein the tumor tissue sample obtained from the patient has been determined to express CD31 and VEGFA at a level that is more than the 75<sup>th</sup> percentile for CD31 and VEGFA expression, respectively, in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

5. The use of claim 1, wherein the gynecologic cancer is selected from the group consisting of ovarian cancer, peritoneal cancer, fallopian tube cancer, cervical cancer, endometrial cancer, vaginal cancer, and vulvar cancer.

6. The use of claim 5, wherein the gynecologic cancer is ovarian cancer.

7. The use of claim 1, wherein the gynecologic cancer is platinum-resistant, platinum-sensitive, advanced, refractory, or recurrent.

8. The use of claim 1, wherein the medicament improves progression free survival (PFS) in the patient.

9. The use of claim 1, wherein the medicament improves overall survival (OS) in the patient.
10. The use of claim 1, wherein the medicament is formulated for use in combination with one or more additional chemotherapeutic agents in a chemotherapy regimen.
11. The use of claim 10, wherein the one or more additional chemotherapeutic agents is selected from the group consisting of: a chemotherapeutic agent, HER antibody, antibody directed against a tumor associated antigen, anti-hormonal compound, cardioprotectant, cytokine, EGFR-targeted drug, anti-angiogenic agent, tyrosine kinase inhibitor, COX inhibitor, non-steroidal anti-inflammatory drug, farnesyl transferase inhibitor, antibody that binds oncofetal protein CA 125, Her2 vaccine, HER targeting therapy, Raf or ras inhibitor, liposomal doxorubicin, topotecan, taxane, dual tyrosine kinase inhibitor, TLK286, EMD-7200, a medicament that treats nausea, a medicament that prevents or treats skin rash or standard acne therapy, a medicament that treats or prevents diarrhea, a body temperature-reducing medicament, and a hematopoietic growth factor.
12. The use of claim 10, wherein the chemotherapeutic agent is gemcitabine, carboplatin, oxaliplatin, irinotecan, fluoropyrimidine, paclitaxel docetaxel, topotecan, capecitabine, leucovorin, temozolomide, interferon-alpha, or liposomal doxorubicin.
13. The use of claim 10, wherein the chemotherapy regimen comprises carboplatin and paclitaxel; carboplatin and gemcitabine; or paclitaxel, topotecan, or pegylated liposomal doxorubicin.
14. The use of claim 10, wherein the chemotherapy regimen comprises capecitabine and paclitaxel; or capecitabine and docetaxel.
15. The use of claim 10, wherein the chemotherapy regimen comprises temozolomide and optionally radiotherapy.
16. The use of claim 10, wherein the chemotherapy regimen comprises fluoropyrimidine, irinotecan, cisplatin, and oxaliplatin; fluoropyrimidine and irinotecan; fluoropyrimidine, leucovorin, and oxaliplatin; or irinotecan, fluoropyrimidine, and leucovorin.

17. The use of claim 10, wherein the chemotherapy regimen comprises paclitaxel and topotecan; or paclitaxel and cisplatin.

18. The use of claim 10, wherein the chemotherapy regimen comprises interferon-alpha2a.

19. The use of claim 1, wherein the VEGF antagonist is an anti-VEGF antibody.

20. The use of claim 19, wherein the anti-VEGF antibody is bevacizumab.

21. The use of claim 1, wherein CD31 and/or VEGFA expression is detected by an immunohistochemical (IHC) method.

22. The use of claim 1, wherein the level of CD31 expression detected in said tumor tissue sample obtained from said patient is used to determine the density of CD31 microvascular structures (CD31 MVD) in said tumor tissue sample obtained from said patient, and optionally wherein CD31 MVD of said tumor tissue sample obtained from said patient is compared to the median level of CD31 MVD in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

23. A method of identifying a patient suffering from a gynecologic cancer who may benefit from administration of a VEGF antagonist, the method comprising:

a) determining the expression level of CD31 and VEGFA in a tumor tissue sample that has been obtained from the patient, wherein expression of CD31 and VEGFA at a level more than the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer indicates that the patient may benefit from administration of a VEGF antagonist, and optionally

b) wherein the VEGF antagonist is to be administered to the patient.

24. A method of predicting responsiveness of a patient to administration of a VEGF antagonist for treatment of a gynecologic cancer, the method comprising:

a) determining the expression level of CD31 and VEGFA in a tumor tissue sample that has been obtained from the patient, wherein expression of CD31 and VEGFA at a level more than the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer indicates that the patient is more likely to be responsive to the administration of the VEGF antagonist, and optionally

b) wherein the VEGF antagonist is to be administered to the patient.

25. The method of claim 23 or 24, wherein the tumor tissue sample obtained from the patient has been determined to express CD31 at a level that is more than the 75<sup>th</sup> percentile for CD31 expression in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

26. The method of claim 23 or 24, wherein the tumor tissue sample obtained from the patient has been determined to express VEGFA at a level that is more than the 75<sup>th</sup> percentile for VEGFA expression in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

27. The method of claim 23 or 24, wherein the tumor tissue sample obtained from the patient has been determined to express CD31 and VEGFA at a level that is more than the 75<sup>th</sup> percentile for CD31 and VEGFA expression, respectively, in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

28. The method of claim 23 or 24, wherein the gynecologic cancer is selected from the group consisting of ovarian cancer, peritoneal cancer, fallopian tube cancer, cervical cancer, endometrial cancer, vaginal cancer, and vulvar cancer.

29. The method of claim 28, wherein the gynecologic cancer is ovarian cancer.

30. The method of claim 23 or 24, wherein the gynecologic cancer is platinum-resistant, platinum-sensitive, advanced, refractory, or recurrent.

31. The method of claim 23 or 24, wherein the tumor tissue sample is one that has been obtained before neoadjuvant or adjuvant therapy.

32. The method of claim 23 or 24, wherein CD31 and/or VEGFA expression is detected by an immunohistochemical (IHC) method.

33. The method of claim 23 or 24, wherein the VEGF antagonist is to be administered in combination with one or more additional chemotherapeutic agents in a chemotherapy regimen.

34. The method of claim 33, wherein the one or more additional chemotherapeutic agents is selected from the group consisting of: a chemotherapeutic agent, HER antibody, antibody directed against a tumor associated antigen, anti-hormonal compound, cardioprotectant, cytokine, EGFR-targeted drug, anti-angiogenic agent, tyrosine kinase inhibitor, COX inhibitor, non-steroidal anti-inflammatory drug, farnesyl transferase inhibitor, antibody that binds oncofetal protein CA 125, Her2 vaccine, HER targeting therapy, Raf or ras inhibitor, liposomal doxorubicin, topotecan, taxane, dual tyrosine kinase inhibitor, TLK286, EMD-7200, a medicament that treats nausea, a medicament that prevents or treats skin rash or standard acne therapy, a medicament that treats or prevents diarrhea, a body temperature-reducing medicament, and a hematopoietic growth factor.

35. The method of claim 34, wherein the chemotherapy regimen comprises carboplatin and paclitaxel.

36. The method of claim 23 or 24, wherein the VEGF antagonist is an anti-VEGF antibody.

37. The method of claim 36, wherein the anti-VEGF antibody is bevacizumab.

38. The method of claim 23 or 24, wherein the level of CD31 expression detected in said sample of said patient is used to determine the density of CD31 microvascular structures (CD31 MVD) in said gynecologic cancer of said patient, and optionally wherein CD31 MVD of said patient's sample is compared to the median level of CD31 MVD in the cancer type.

39. A method for the prognosis of a patient suffering from a gynecologic cancer, the method comprising:

a) determining the expression level of CD31 and VEGFA in a tumor tissue sample that has been obtained from the patient,

b) comparing the expression level of CD31 and VEGFA to the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer, and

c) determining a prognosis for the patient, wherein a poor prognosis is determined when expression of CD31 and VEGFA in the tumor tissue sample obtained from the patient is at a level more than the median level for CD31 and VEGFA expression, respectively, in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

40. The method of claim 39, wherein said method is carried out prior to administration of an anti-cancer agent to the patient in order to provide a pre-administration prognosis of survival.

41. The method of claim 39, further comprising the step of identifying the patient as likely to benefit from administration of a VEGF antagonist when the patient is determined to have a poor prognosis of survival.

42. The method of claim 39, wherein a VEGF antagonist is to be administered to the patient, if the patient is determined to have a poor prognosis.

43. The method of claim 39, wherein the survival is progression free survival or overall survival.

44. The method of claim 39, wherein the VEGF antagonist is an anti-VEGF antibody.

45. The method of claim 44, wherein the anti-VEGF antibody is bevacizumab.

46. The method of claim 39, wherein the level of CD31 expression detected in said tumor tissue sample obtained from said patient is used to determine the density of CD31 microvascular structures (CD31 MVD) in said tumor tissue sample obtained from said patient, and optionally wherein CD31 MVD of said tumor tissue sample obtained from said patient is compared to the median level of CD31 MVD in the tumor tissue samples obtained from the population of patients having the gynecologic cancer.

47. A VEGF antagonist for use in treating a gynecologic cancer in a patient, wherein a tumor tissue sample obtained from the patient has been determined to express CD31 and VEGFA at a level more than the median level for CD31 and VEGFA expression, respectively, in tumor tissue samples obtained from a population of patients having the gynecologic cancer.