

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 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. 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 cancer in a patient, 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 another aspect, there is provided a method of identifying a patient suffering from a cancer who may benefit from administration of a VEGF antagonist, the method including: a) determining the expression level of CD31 and/or tumor VEGFA in a sample that has been obtained from the patient, wherein expression of 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 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 cancer, the method including: a) determining the expression level of CD31 and/or tumor VEGFA in a sample that has been obtained from the patient, wherein expression of 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 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.

In certain embodiments, the sample is a tumor tissue sample. In other embodiments, the sample is obtained before neoadjuvant or adjuvant therapy.

5 In a further embodiment, the patient's cancer has been determined to express CD31 at a level that is more 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 more than the 75th percentile for CD31 expression in the cancer type.

10 In yet another embodiment, the patient's cancer has been determined to express tumor VEGFA at a level that is more 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 more than the 75th percentile for tumor VEGFA expression in the cancer type.

15 In one particular embodiment, the administration of the VEGF antagonist improves progression free survival (PFS) in the patient. In a second particular embodiment, the administration of the VEGF antagonist improves overall survival (OS) in the patient. In a third particular embodiment, the VEGF antagonist is administered in combination with one or more additional chemotherapeutic agents in a chemotherapy regimen.

20 In some embodiments, 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
25 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. In some preferred embodiments, the chemotherapeutic agent is gemcitabine, carboplatin, oxaliplatin, irinotecan, fluoropyrimidine (e.g., 5-FU), paclitaxel (e.g., nab-paclitaxel), docetaxel, topotecan, capecitabine, lecovorin, temozolomide, interferon-alpha, or liposomal doxorubicin
30 (e.g., pegylated liposomal doxorubicin).

In certain embodiments, the chemotherapy regimen includes the administration of carboplatin and paclitaxel; carboplatin and gemcitabine; or paclitaxel, topotecan, or pegylated

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 cancer, the method including: a) determining the expression level of CD31 in a sample that has been obtained from the patient, b) comparing the expression level of CD31 to the median level for CD31 in the cancer type, and c) determining a prognosis for the patient, wherein a poor prognosis is when expression of CD31 is at a level more than the median level for CD31 expression.

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. In another aspect, there is provided 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. In another aspect, there is provided 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 25th 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 25th 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 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,
5 respectively, in the cancer type.
2. The use of claim 1, wherein the patient's cancer has been determined to express CD31 at a level that is more than the median level for CD31 expression in the cancer type.
- 10 3. The use of claim 1 or 2, wherein the patient's cancer has been determined to express CD31 at a level that is more than the 75th percentile for CD31 expression in the cancer type.
4. The use of any one of claims 1-3, wherein the patient's cancer has been determined to express tumor VEGFA at a level that is more than the median level for tumor VEGFA
15 expression in the cancer type.
5. The use of any one of claims 1-4, wherein the patient's cancer has been determined to express tumor VEGFA at a level that is more than the 75th percentile for tumor VEGFA
20 expression in the cancer type.
6. The use of any one of claims 1-5, wherein 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).
- 25 7. The use of any one of claims 1-6, wherein 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.
8. The use of claim 7, wherein the gynecologic cancer is ovarian cancer.
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9. The use of any one of claims 1-8, wherein the cancer is platinum-resistant, platinum-sensitive, advanced, refractory, or recurrent.

10. The use of any one of claims 1-9, wherein the medicament improves progression free survival (PFS) in the patient.

11. The use of any one of claims 1-10, wherein the medicament improves overall survival (OS) in the patient.

12. The use of any one of claims 1-11, wherein the medicament is formulated for use in combination with one or more additional chemotherapeutic agents in a chemotherapy regimen.

13. The use of claim 12, 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.

14. The use of claim 12, wherein the chemotherapeutic agent is gemcitabine, carboplatin, oxaliplatin, irinotecan, fluoropyrimidine (e.g., 5-FU), paclitaxel (e.g., nab-paclitaxel), docetaxel, topotecan, capecitabine, lecovorin, temozolomide, interferon-alpha, or liposomal doxorubicin (e.g., pegylated liposomal doxorubicin).

15. The use of claim 12, wherein the chemotherapy regimen comprises carboplatin and paclitaxel; carboplatin and gemcitabine; or paclitaxel, topotecan, or pegylated liposomal doxorubicin.

16. The use of claim 12, wherein the chemotherapy regimen comprises capecitabine and paclitaxel; or capecitabine and docetaxel.

17. The use of claim 12, wherein the chemotherapy regimen comprises temozolomide and optionally radiotherapy.

18. The use of claim 12, wherein the chemotherapy regimen comprises fluropyrimidine, irinotecan, cisplatin, fluropyrimidine and oxaliplatin; fluropyrimidine and irinotecan; fluropyrimidine, lecovorin, and oxaliplatin; or ironotecan, fluoropyrimidine, and leucovorin.

19. The use of claim 12, wherein the chemotherapy regimen comprises paclitaxel and topotecan; or paclitaxel and cisplatin.

20. The use of claim 12, wherein the chemotherapy regimen comprises interferon-alpha2a.

21. The use of any one of claims 1-20, wherein the VEGF antagonist is an anti-VEGF antibody.

22. The use of claim 21, wherein the anti-VEGF antibody is bevacizumab.

23. The use of any one of claims 1-22, wherein CD31 and/or tumor VEGFA expression is detected by an immunohistochemical (IHC) method.

24. The use of any one of claims 1-23, wherein the level of CD31 expression detected in said cancer of said patient is used to determine the density of CD31 microvascular structures (CD31 MVD) in said cancer of said patient, and optionally wherein CD31 MVD of said patient's cancer is compared to the median level of CD31 MVD in the cancer type.

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

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

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

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

27. The method of claim 25 or 26, wherein the patient's cancer has been determined to express CD31 at a level that is more than the median level for CD31 expression in the cancer type.

28. The method of any one of claims 25-27, wherein the patient's cancer has been determined to express CD31 at a level that is more than the 75th percentile for CD31 expression in the cancer type.

29. The method of any one of claims 25-28, wherein the patient's cancer has been determined to express tumor VEGFA at a level that is more than the median level for tumor VEGFA expression in the cancer type.

30. The method of any one of claims 25-29, wherein the patient's cancer has been determined to express tumor VEGFA at a level that is more than the 75th percentile for tumor VEGFA expression in the cancer type.

31. The method of any one of claims 25-30, wherein 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.

32. The method of claim 31, wherein the gynecologic cancer is ovarian cancer.

33. The method of any one of claims 25-32, wherein the cancer is platinum-resistant, platinum-sensitive, advanced, refractory, or recurrent.

34. The method of any one of claims 25-33, wherein the sample is a tumor tissue sample.

35. The method of any one of claims 25-34, wherein the sample is one that has been obtained before neoadjuvant or adjuvant therapy.

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36. The method of any one of claims 25-35, wherein CD31 and/or tumor VEGFA expression is detected by an immunohistochemical (IHC) method.

37. The method of any one of claims 25-36, wherein the VEGF antagonist is to be administered in combination with one or more additional chemotherapeutic agents in a chemotherapy regimen.

38. The method of claim 37, 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.

39. The method of claim 37, wherein the chemotherapy regimen comprises carboplatin and paclitaxel.

40. The method of any one of claims 25-39, wherein the VEGF antagonist is an anti-VEGF antibody.

41. The method of claim 40, wherein the anti-VEGF antibody is bevacizumab.

42. The method of any one of claims 25-41, 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 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.

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

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

b) comparing the expression level of CD31 to the median level for CD31 in the cancer type, and

c) determining a prognosis for the patient, wherein a poor prognosis is when expression of CD31 is at a level more than the medial level for CD31 expression.

44. The method of claim 43, wherein said method is carried out prior to administration of an anti-cancer agent in order to provide a pre-administration prognosis of survival.

45. The method of claim 43 or 44, 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.

46. The method of any one of claims 43-45, wherein a VEGF antagonist is to be administered to the patient, if the patient is determined to have a poor prognosis.

47. The method of any one of claims 43-46, wherein the survival is progression free survival or overall survival.

48. The method of any one of claims 43-47, wherein the VEGF antagonist is an anti-VEGF antibody.

49. The method of claim 48, wherein the anti-VEGF antibody is bevacizumab.

50. The method of any one of claims 43-49, 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 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.

51. 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.

5 52. The use of claim 51, wherein 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.

53. The use of claim 52, wherein the patient's cancer has been determined to express CD31 at a level that is less than the 25th percentile for CD31 expression in the cancer type.

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54. The use of claim 51, wherein 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.

15 55. The use of claim 54, wherein the patient's cancer has been determined to express tumor VEGFA at a level that is less than the 25th percentile for tumor VEGFA expression in the cancer type.

20 56. The use of any one of claims 51-55, wherein 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).

25 57. The use of any one of claims 51-55, wherein 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.

58. The use of claim 57, wherein the gynecologic cancer is ovarian cancer.

30 59. The use of any one of claims 51-58, 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 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.

60. 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 more than the median level for CD31 and/or tumor VEGFA expression, respectively, in the cancer type.

- 5 61. 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.