

Accordingly, there is a need for methods of determining whether patients are likely to respond to chemotherapeutic-based therapies, and also to develop alternative strategies for the treatment of cancer in general.

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SUMMARY

Disclosed are methods of identifying patients with cancer that is chemotherapy-resistant, the methods including: a) determining the expression level of one or more stroma signature gene(s) in a sample obtained from a patient, b) comparing the expression level of the one or more stroma signature gene(s) to the median level of expression for the one or more stroma signature gene(s) in the cancer type, and c) determining if the patient's cancer is chemotherapy-resistant, wherein expression of the one or more stroma signature gene(s) in the patient sample at a level more than the median level for expression of the one or more stroma signature gene(s) in the cancer type indicates that the patient has cancer that is chemotherapy-resistant, e.g., in the case of detecting expression levels of one or more stroma signature genes that are up-regulated in chemotherapy (e.g., platinum-based chemotherapy)-resistant cancer. Disclosed is a method of identifying a patient with cancer that is chemotherapy-resistant, the method comprising

10 a) determining the expression level of one or more stroma signature gene(s) in a sample that has been obtained from the patient,

b) comparing the expression level of the one or more stroma signature gene(s) to the

20 median level of expression for the one or more stroma signature gene(s) in the cancer type, and

c) determining if the patient's cancer is chemotherapy-resistant, wherein expression of the one or more stroma signature gene(s) in the patient sample at a level more than the median level for expression of the one or more stroma signature gene(s) in the cancer type indicates that the patient has cancer that is chemotherapy-resistant.

25 Detection of decreased levels of expression (e.g., a level less than the median level) can also indicate that the patient has cancer that is chemotherapy-resistant, in the case of detecting expression levels of one or more stroma signature genes that are down-regulated in chemotherapy (e.g., platinum-based chemotherapy)-resistant cancer.

In one example, the patient has cancer that is chemotherapy-resistant if the patient's

30 cancer has been determined to express the one or more stroma signature gene(s) at a level that is more than the 75th percentile for the one or more stroma signature gene(s) expression in the cancer type (e.g., in the case of one or more stroma signature genes that are up-regulated in chemotherapy (e.g., platinum-based chemotherapy)-resistant cancer). In certain other examples, the cancer that is chemotherapy-resistant is cancer that is platinum-resistant.

35 In certain examples, the methods further include the step of identifying the patient as likely to benefit from administration of a VEGF antagonist when the patient is determined to have cancer that is chemotherapy-resistant. In certain other examples, the methods further include the step of administering a VEGF antagonist in a therapeutically effective amount to the patient, if the patient is determined to have cancer that is chemotherapy-resistant. In preferred

40 examples, the VEGF antagonist is an anti-VEGF antibody. Preferably, the anti-VEGF antibody is bevacizumab.

In other examples, the methods further include the step of identifying the patient as likely to benefit from a stroma-targeted therapy when the patient is determined to have cancer that is chemotherapy-resistant. In yet other examples, the methods further include the step of administering a stroma-targeted agent in a therapeutically effective amount to the patient, if the patient is determined to have cancer that is chemotherapy-resistant.

In another example, the methods further include the step of identifying the patient as likely to benefit from an immunotherapy when the patient is determined to have cancer that is chemotherapy-resistant. In yet another example, the methods further include the step of administering an immunomodulatory agent in a therapeutically effective amount to the patient, if the patient is determined to have cancer that is chemotherapy-resistant. In preferred examples, the immunomodulatory agent includes a TDO2, CD36, GZMK, CD247, CD1C, CSF1, IDO1, IL7R, or CCR7 antagonist.

Disclosed are methods of identifying patients with cancer that is chemotherapy-sensitive, the methods including: a) determining the expression level of one or more stroma signature gene(s) in a sample obtained from a patient, b) comparing the expression level of the one or more stroma signature gene(s) to the median level of expression for the one or more stroma signature gene(s) in the cancer type, and c) determining if the patient has cancer that is chemotherapy-sensitive, wherein expression of the one or more stroma signature gene(s) in the patient sample at a level less than the median level for expression of the one or more stroma signature gene(s) in the cancer type indicates that the patient has cancer that is chemotherapy-sensitive (e.g., in the case of one or more stroma signature genes that are up-regulated in chemotherapy (e.g., platinum-based chemotherapy)-resistant cancer). Disclosed is a method of identifying a patient with cancer that is chemotherapy-sensitive, the method comprising

a) determining the expression level of one or more stroma signature gene(s) in a sample that has been obtained from the patient,

b) comparing the expression level of the one or more stroma signature gene(s) to the median level of expression for the one or more stroma signature gene(s) in the cancer type, and

c) determining if the patient has cancer that is chemotherapy-sensitive, wherein expression of the one or more stroma signature gene(s) in the patient sample at a level less than the median level for expression of the one or more stroma signature gene(s) in the cancer type indicates that the patient has cancer that is chemotherapy-sensitive.

In certain examples, the patient has cancer that is chemotherapy-sensitive if the patient's cancer has been determined to express the one or more stroma signature gene(s) at a level that is less than the 25th percentile for the one or more stroma signature gene(s) expression in the cancer type. In other examples, the method includes the step of administering one or more chemotherapeutic agent(s) in a chemotherapy regimen, if the patient is determined to have cancer that is chemotherapy-sensitive.

In certain examples, the sample is a tumor tissue sample. In particular examples, the methods are carried out prior to administering a chemotherapeutic agent in order to provide a pre-administration diagnosis. In certain examples, the patient has not undergone chemotherapy or the patient is currently undergoing chemotherapy.

Disclosed are methods of identifying patients suffering from cancer who may benefit from administration of a VEGF antagonist or an immunomodulatory agent, the methods including: a) determining the expression level of one or more stroma signature gene(s) in a sample obtained from a patient, wherein expression of the one or more stroma signature gene(s) at a level more than the median level for expression of the one or more stroma signature gene(s) in the cancer type indicates that the patient may benefit from administration of a VEGF antagonist or immunomodulatory agent (e.g., in the case of one or more stroma signature genes that are up-regulated in chemotherapy (e.g., platinum-based chemotherapy)-resistant cancer), and optionally b) administering the VEGF antagonist or immunomodulatory agent in a therapeutically effective amount to the patient. In one aspect, the present disclosure refers to a method of identifying a patient suffering from a platinum-resistant cancer who may benefit from administration of a VEGF antagonist, the method comprising:

(a) determining the expression level of one or more stroma signature gene(s) in a sample that has been obtained from the patient, wherein expression of the one or more stroma signature gene(s) at a level more than the median level for expression of the one or more stroma signature gene(s) in the cancer type indicates that the patient may benefit from administration of a VEGF antagonist, wherein the one or more stroma signature gene(s) includes periostin (POSTN), and wherein optionally

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

In another aspect, the present disclosure refers to use of a VEGF antagonist in the manufacture of a medicament for treating a patient suffering from a platinum-resistant cancer, wherein the patient's cancer has been determined to express one or more stroma signature gene(s) at a level more than the median level for expression of the one or more stroma signature gene(s) in the cancer type, wherein the one or more stroma signature gene(s) includes periostin (POSTN).

In particular examples, the above methods further include the step of administering one or more chemotherapeutic agents in a chemotherapy regimen. In some examples, the chemotherapeutic agent(s) is selected from the group consisting of a HER antibody, an antibody directed against a tumor associated antigen, an anti-hormonal compound, a cardioprotectant, a cytokine, an EGFR-targeted drug, an anti-angiogenic agent, a tyrosine kinase inhibitor, a COX inhibitor, a non-steroidal anti-inflammatory drug, a farnesyl transferase inhibitor, an antibody that binds oncofetal protein CA 125, a Her2 vaccine, a HER targeting therapy, a 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. In other examples, the one or more chemotherapeutic agent(s) 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).

In one preferred example, the chemotherapy regimen includes the administration of carboplatin and paclitaxel; carboplatin and gemcitabine; or paclitaxel, topotecan, or pegylated liposomal doxorubicin. In a second preferred example, the chemotherapy regimen includes the administration of capecitabine and paclitaxel; or capecitabine and docetaxel. In a third preferred example, the chemotherapy regimen includes the administration of temozolomide and optionally radiotherapy. In a fourth preferred example, the chemotherapy regimen includes the administration of fluoropyrimidine, irinotecan, cisplatin, fluoropyrimidine and oxaliplatin; fluoropyrimidine and irinotecan; fluoropyrimidine, lecovorin, and oxaliplatin; or irinotecan, fluoropyrimidine, and leucovorin. In a fifth preferred example, the chemotherapy regimen includes the administration of paclitaxel and topotecan; or paclitaxel and

cisplatin. In a sixth preferred example, the chemotherapy regimen includes the administration of interferon-alpha2a.

In some examples, the one or more stroma signature gene is selected from the group consisting of POSTN, LOX, TIMP3, FAP, BGN, FGF1, FN1, ANGPTL2, ACTA2, MMP11, RBP4, CD36, PLVAP, PECAM1, GZMK, CD247, ABCC9, PCOLCE, CD1C, MS4A1, CD44, PMEPA1, IL7R, FBLN1, TWIST1, ID1, RAC2, GFRA1, CCR7, MAN1A1, EVI2A, PTPRC CD45RA, FCRL5, NNMT, CD27, SLA, TDO2, NUA1, and COL4A1. In preferred examples, the stroma signature gene is POSTN. In other preferred examples, the one or more stroma signature gene(s) is POSTN and FAP; POSTN and TIMP3; POSTN and LOX; POSTN, FAP, and TIMP3; POSTN, FAP, and LOX; POSTN, TIMP3, and LOX; or POSTN, FAP, TIMP3, and LOX.

Disclosed is a method of treating a patient with cancer, the method including administering to the patient a therapeutically effective amount of a stroma-targeted agent, wherein the patient's cancer has been determined to express one or more stroma signature gene(s) at a level more than the median level for expression of the one or more stroma signature gene(s) in the cancer type. Disclosed is use of a stroma-targeted agent in the manufacture of a medicament for treating cancer in a patient, wherein the patient's cancer has been determined to express one or more stroma signature gene(s) at a level more than the median level for expression of the one or more stroma signature gene(s) in the cancer type.

In preferred examples of the above methods, the stroma-targeted agent is an anti-periostin (POSTN) antibody. In certain examples of the above methods, the cancer is primary, advanced, refractory, or recurrent. In other examples, 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 examples, the gynecologic cancer is ovarian cancer. In yet other examples of the above methods, 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).

Disclosed are methods of determining the stage of ovarian cancer in a patient. The methods include determining the expression level of POSTN in a sample (e.g., a tumor tissue sample, a blood sample, or a serum sample) obtained from the patient. Detection of an increased level of expression of POSTN in the patient sample, relative to a control, indicates an advanced stage of ovarian cancer (e.g., FIGO ovarian cancer stage III or IV). Disclosed is a method of determining the stage of ovarian cancer in a patient, the method comprising determining the expression level of POSTN in a sample that has been obtained from the patient, wherein detection of an increased level of expression of POSTN in the patient sample, relative to a control, indicates an advanced stage of ovarian cancer. In certain examples, the control is the median level of POSTN expression in a population of patients having ovarian cancer, while in other examples, the control is the median level of POSTN expression in a population of patients having FIGO stage I and/or FIGO

CLAIMS

1. A method of identifying a patient suffering from a platinum-resistant cancer who may benefit from administration of a VEGF antagonist, the method comprising:

- 5 (a) determining the expression level of one or more stroma signature gene(s) in a sample that has been obtained from the patient, wherein expression of the one or more stroma signature gene(s) at a level more than the median level for expression of the one or more stroma signature gene(s) in the cancer type indicates that the patient may benefit from administration of a VEGF antagonist, wherein the one or more stroma signature gene(s) includes periostin (POSTN), and wherein optionally
- 10 (b) the patient is to be administered the VEGF antagonist.

2. The method of claim 1, wherein the VEGF antagonist is an anti-VEGF antibody.

3. The method of claim 2, wherein the anti-VEGF antibody is bevacizumab.

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4. The method of any one of claims 1-3, wherein one or more chemotherapeutic agent(s) is/are to be administered to the patient.

5. The method of any one of claims 1-4, wherein the patient's cancer has been determined to
20 express the one or more stroma signature gene(s) at a level that is more than the 75th percentile for the one or more stroma signature gene(s) expression in the cancer type.

6. The method of any one of claims 1-5, wherein the one or more stroma signature gene(s) includes one or more additional stroma signature genes selected from the group consisting of
25 LOX, TIMP3, FAP, BGN, FGF1, FN1, ANGPTL2, ACTA2, MMP11, RBP4, CD36, PLVAP, PECAM1, GZMK, CD247, ABCC9, PCOLCE, CD1C, MS4A1, CD44, PMPA1, IL7R, FBLN1, TWIST1, ID1, RAC2, GFRA1, CCR7, MAN1A1, EVI2A, PTPRC CD45RA, FCRL5, NNMT, CD27, SLA, TDO2, NUA1, and COL4A1.

7. The method of any one of claims 1-6, wherein the stroma signature genes are POSTN, FAP, and LOX; POSTN and FAP; POSTN and TIMP3; POSTN and LOX; POSTN, FAP, and TIMP3; POSTN, TIMP3, and LOX; or POSTN, FAP, TIMP3, and LOX.

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8. The method of claim 7, wherein the stroma signature genes are POSTN, FAP, and LOX.

9. The method of any one of claims 1-8, wherein the cancer is a gynecologic cancer.

10 10. The method of claim 9, wherein the gynecologic cancer is ovarian cancer, peritoneal cancer, fallopian tube cancer, cervical cancer, endometrial cancer, vaginal cancer, or vulvar cancer.

11. The method of any one of claims 1-8, wherein the cancer is selected from the group consisting of colorectal cancer, breast cancer, non-small cell lung cancer (NSCLC), kidney
15 cancer (renal cell carcinoma), or brain cancer (glioblastoma).

12. The method of any one of claims 1-11, wherein the sample is a tumor tissue sample, a blood sample, or a serum sample.

20 13. Use of a VEGF antagonist in the manufacture of a medicament for treating a patient suffering from a platinum-resistant cancer, wherein the patient's cancer has been determined to express one or more stroma signature gene(s) at a level more than the median level for expression of the one or more stroma signature gene(s) in the cancer type, wherein the one or more stroma signature gene(s) includes periostin (POSTN).

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14. The use of claim 13, wherein the VEGF antagonist is an anti-VEGF antibody.

15. The use of claim 14, wherein the anti-VEGF antibody is bevacizumab.

16. The use of any one of claims 13-15, wherein the medicament is formulated for
5 administration with one or more chemotherapeutic agent(s).

17. The use of any one of claims 13-16, wherein the patient's cancer has been determined to
express the one or more stroma signature gene(s) at a level that is more than the 75th percentile
for the one or more stroma signature gene(s) expression in the cancer type.

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18. The use of any one of claims 13-17, wherein the one or more stroma signature gene(s)
includes one or more additional stroma signature genes selected from the group consisting of
LOX, TIMP3, FAP, BGN, FGF1, FN1, ANGPTL2, ACTA2, MMP11, RBP4, CD36, PLVAP,
PECAM1, GZMK, CD247, ABCC9, PCOLCE, CD1C, MS4A1, CD44, PMEPA1, IL7R,
15 FBLN1, TWIST1, ID1, RAC2, GFRA1, CCR7, MAN1A1, EVI2A, PTPRC CD45RA, FCRL5,
NNMT, CD27, SLA, TDO2, NUA1, and COL4A1.

19. The use of any one of claims 13-18, wherein the stroma signature genes are POSTN, FAP,
and LOX; POSTN and FAP; POSTN and TIMP3; POSTN and LOX; POSTN, FAP, and TIMP3;
20 POSTN, TIMP3, and LOX; or POSTN, FAP, TIMP3, and LOX.

20. The use of claim 19, wherein the stroma signature genes are POSTN, FAP, and LOX.

21. The use of any one of claims 13-20, wherein the cancer is a gynecologic cancer.

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22. The use of claim 21, wherein the gynecologic cancer is ovarian cancer, peritoneal cancer, fallopian tube cancer, cervical cancer, endometrial cancer, vaginal cancer, or vulvar cancer.
- 5 23. The use of any one of claims 13-22, 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).
- 10 24. The use of any one of claims 13-23, wherein the sample is a tumor tissue sample, a blood sample, or a serum sample.