

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. In one aspect, there is provided a method of identifying a patient with cancer that is chemotherapy-resistant, 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'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.

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 embodiment, the patient has cancer that is chemotherapy-resistant if 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 (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 embodiments of the above aspect, the cancer that is chemotherapy-resistant is cancer that is platinum-resistant.

In certain embodiments, 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 embodiments, 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 embodiments, the VEGF antagonist is an anti-VEGF antibody. Preferably, the anti-VEGF antibody is bevacizumab.

In other embodiments, 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 embodiments, 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 embodiment, 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 embodiment, 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 embodiments, 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). In another aspect, there is provided 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 embodiments, 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 embodiments, 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 embodiments of the above aspects and embodiments, the sample is a tumor tissue sample. In particular embodiments, the methods are carried out prior to administering a chemotherapeutic agent in order to provide a pre-administration diagnosis. In certain embodiments, 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 another aspect, there is provided a method of identifying a patient suffering from cancer who may benefit from administration of a VEGF antagonist or an immuno-modulatory agent, 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 or immunomodulatory agent, and wherein optionally

b) the patient is to be administered the VEGF antagonist or immunomodulatory agent.

In particular embodiments, the above methods further include the step of administering one or more chemotherapeutic agents in a chemotherapy regimen. In some embodiments, 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 embodiments, 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 embodiment, the chemotherapy regimen includes the administration of carboplatin and paclitaxel; carboplatin and gemcitabine; or paclitaxel, topotecan, or pegylated liposomal doxorubicin. In a second preferred embodiment, the chemotherapy regimen includes the administration of capecitabine and paclitaxel; or capecitabine and docetaxel. In a third preferred embodiment, the chemotherapy regimen includes the administration of temozolomide and optionally radiotherapy. In a fourth preferred embodiment, 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 embodiment, the chemotherapy regimen includes the administration of paclitaxel and topotecan; or paclitaxel and

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

In some embodiments, 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
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embodiments, the stroma signature gene is POSTN. In other preferred embodiments, 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
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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 another aspect, there is provided 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 embodiments of the above methods, the stroma-targeted agent is an anti-periostin (POSTN) antibody. In certain embodiments of the above methods, the cancer is primary, advanced, refractory, or recurrent. In other embodiments, 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
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embodiments, the gynecologic cancer is ovarian cancer. In yet other embodiments 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). In another aspect, there is provided 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
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embodiments, the control is the median level of POSTN expression in a population of patients having ovarian cancer, while in other embodiments, the control is the median level of POSTN expression in a population of patients having FIGO stage I and/or FIGO

stage II ovarian cancer. Optionally, the methods also include a step of administering a therapy to the patient, if the patient is determined to have ovarian cancer that is in an advanced stage.

Other features and advantages of the disclosure will be apparent from the detailed description, the drawings, and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

5 **Figures 1A-1D** show the identification of a “reactive stroma” gene signature up-regulated in primary chemotherapy-resistant ovarian tumors. **(A)** Hierarchical clustering of the top 14 most differentially expressed genes (false discovery rate (FDR) $\leq 10\%$, fold change ≥ 1.5) between 32 Plat-R primary and 26 Plat-S primary ovarian tumors. Clinically defined response to primary chemotherapy, TP53 mutation status, and 7 recurrently amplified genes (≥ 4 copies) are annotated at the bottom; **(B)** Hierarchical clustering of the top 65 most differentially expressed
10 genes (FDR $\leq 10\%$, fold change ≥ 1.5) between 27 patient-matched Plat-R primary and Plat-R recurrent ovarian tumors; **(C)** Venn diagram of common signature genes significantly differentially expressed in Plat-R primary and recurrent tumors; **(D)** Gene expression of the four reactive stroma signature genes in 26 Plat-S primary, 32 Plat-R primary, and 27 Plat-R recurrent
15 tumors.

Figure 2 is a series of plots showing mRNA expression levels of the four reactive stroma signature genes that are highly correlated with one another.

Figures 3A-3B show in situ analysis of the reactive stroma signature genes POSTN, LOX, and FAP by RNA ISH and IHC. **(A)** Representative ISH and IHC images from a Plat-S
20 primary tumor, a patient-matched Plat-R primary tumor prior to chemotherapy, and recurrent tumors post chemotherapy at disease progression. Images in the left two columns: 2-plex chromogenic RNA ISH for detection of POSTN, LOX, and singleplex RNA ISH for detection of FAP mRNA localization. Images in the right three columns: IHC staining for POSTN, FAP, and aSMA protein localization. Bar = 100um. **(B)** Summary of ISH scores and IHC scores in all 85
25 samples (POSTN and FAP ISH) or five representative tumor specimens (LOX ISH, POSTN, and FAP IHC) from each of the response group: Plat-S primary, patient-matched Plat-R primary, and recurrent tumors. Both ISH H-score (Material and Methods, plotted with means and standard deviations) and IHC overall score were determined in tumor and stromal cells respectively. * $p < 0.05$, ** $p < 0.01$.

30 **Figures 4A-4C** show that POSTN expression levels are correlated with the desmoplasia phenotype *in vivo*, and that POSTN promotes chemotherapy-resistance in EOC cells *in vitro*. **(A)** Increased desmoplasia is correlated with POSTN expression and primary chemotherapy-

CLAIMS

1. A method of identifying a patient with cancer that is chemotherapy-resistant, 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'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.

2. The method of claim 1, wherein the patient has cancer that is chemotherapy-resistant if 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.

3. The method of claim 1 or 2, wherein 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.

4. The method of claim 3, wherein the stroma signature gene is POSTN.

5. The method of claim 3, wherein 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.

6. The method of any one of claims 1-5, wherein the sample is a tumor tissue sample, a blood sample, or a serum sample.

7. The method of any one of claims 1-6, wherein the cancer that is chemotherapy-resistant is

cancer that is platinum-resistant.

8. The method of any one of claims 1-7, wherein the method is carried out prior to administration of a chemotherapeutic agent in order to provide a pre-administration diagnosis.

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9. The method of any one of claims 1-7, wherein the patient has not undergone chemotherapy or wherein the patient is currently undergoing chemotherapy.

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10. The method of any one of claims 1-9, 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 cancer that is chemotherapy-resistant.

11. The method of any one of claims 1-10, wherein if the patient is determined to have cancer that is chemotherapy-resistant, the patient is to be administered a VEGF antagonist.

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12. The method of claim 11, wherein the VEGF antagonist is an anti-VEGF antibody.

13. The method of claim 12, wherein the anti-VEGF antibody is bevacizumab.

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14. The method of any one of claims 1-13, further comprising 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.

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15. The method of any one of claims 1-14, wherein if the patient is determined to have a cancer that is chemotherapy-resistant, the patient is to be administered a stroma-targeted agent.

16. The method of claim 15, wherein the stroma-targeted agent is an anti-periostin (POSTN) antibody.

17. The method of any one of claims 1-16, further comprising 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.

5 18. The method of any one of claims 1-17, wherein if the patient is determined to have cancer that is chemotherapy-resistant, the patient is to be administered an immunomodulatory agent.

19. The method of claim 18, wherein the immunomodulatory agent comprises a TDO2, CD36, GZMK, CD247, CD1C, CSF1R, IDO1, IL7R, or CCR7 antagonist.

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20. The method of any one of claims 1-19, wherein the cancer is primary, advanced, refractory, or recurrent.

15 21. The method of any one of claims 1-20, 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.

22. The method of claim 21, wherein the gynecologic cancer is ovarian cancer.

20 23. The method of any one of claims 1-20, 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 24. 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

30 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.

25. The method of claim 24, wherein 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.

26. The method of claim 24 or 25, wherein 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.

27. The method of claim 26, wherein the stroma signature gene is POSTN.

28. The method of claim 26, wherein 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.

29. The method of any one of claims 24-28, wherein the sample is a tumor tissue sample, a blood sample, or a serum sample.

30. The method of any one of claims 24-29, wherein if the patient is determined to have cancer that is chemotherapy-sensitive, the patient is to be administered one or more chemotherapeutic agent(s) in a chemotherapy regimen.

31. The method of claim 30, wherein the one or more 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.

32. The method of claim 30, wherein 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).
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33. The method of claim 30, wherein the chemotherapy regimen comprises carboplatin and paclitaxel; carboplatin and gemcitabine; or paclitaxel, topotecan, or pegylated liposomal doxorubicin.
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34. The method of claim 30, wherein the chemotherapy regimen comprises capecitabine and paclitaxel; or capecitabine and docetaxel.
35. The method of claim 30, wherein the chemotherapy regimen comprises temozolomide and optionally radiotherapy.
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36. The method of claim 30, wherein the chemotherapy regimen comprises fluoropyrimidine, irinotecan, cisplatin, fluoropyrimidine and oxaliplatin; fluoropyrimidine and irinotecan; fluoropyrimidine, lecovorin, and oxaliplatin; or irinotecan, fluoropyrimidine, and leucovorin.
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37. The method of claim 30, wherein the chemotherapy regimen comprises paclitaxel and topotecan; or paclitaxel and cisplatin.
38. The method of claim 30, wherein the chemotherapy regimen comprises interferon-alpha2a.
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39. The method of any one of claims 1-19, wherein the cancer is primary, advanced, refractory, or recurrent.
40. The method of any one of claims 24-39, 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.
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41. The method of claim 40, wherein the gynecologic cancer is ovarian cancer.

42. The method of any one of claims 24-39, 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).

43. A method of identifying a patient suffering from cancer who may benefit from administration of a VEGF antagonist or an immuno-modulatory agent, 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 or immunomodulatory agent, and wherein optionally

b) the patient is to be administered the VEGF antagonist or immunomodulatory agent.

44. The method of claim 43, 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 43, wherein the immunomodulatory agent comprises a TDO2, CD36, GZMK, CD247, CD1C, CSF1R, IDO1, IL7R, or CCR7 antagonist.

47. 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.

48. The method of any one of claims 43-46 or the use of claim 47, wherein one or more chemotherapeutic agent(s) is/are to be administered to the patient.

49. The method of any one of claims 43-46 or the use of claim 47 or 48, 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.

50. The method of any one of claims 43-46 or the use of any one of claims 47-49, wherein the one or more stroma signature gene(s) 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.

51. The method or use of claim 50, wherein the stroma signature gene is POSTN.

52. The method or use of claim 50, wherein 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.

53. The method of any one of claims 43-46, the use of any one of claims 47-49, or the method or use of claim 51 or 52, wherein the cancer is chemotherapy-resistant, chemotherapy-sensitive, primary, advanced, refractory, or recurrent.

54. The method of any one of claims 43-46, the use of any one of claims 47-49, or the method or use of any one of claims 51-53, 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.

55. The method or use of claim 54, wherein the gynecologic cancer is ovarian cancer.

56. The method of any one of claims 43-46, the use of any one of claims 47-49, or the method or use of any one of claims 51-53, 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).

57. 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.

5 58. The method of claim 57, wherein said control is the median level of POSTN expression in a population of patients having ovarian cancer.

59. The method of claim 57, wherein said control is the median level of POSTN expression in a population of patients having FIGO stage I or FIGO stage II ovarian cancer.

10 60. The method of claim 57, wherein if the patient is determined to have ovarian cancer that is in the advanced stage, the patient is to be administered a therapy.

61. The method of claim 57, wherein ovarian cancer in the advanced stage is FIGO Ovarian Cancer Stage III or IV.

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62. The method of any one of claims 57-61, wherein the sample is a tumor tissue sample, a blood sample, or a serum sample.