

CLAIMS

1. A method for predicting a subject's responsiveness to an anti-angiogenic therapeutic agent comprising:

measuring expression levels of a biomarker panel from a test sample obtained from a subject, in which the biomarker panel comprises one or more biomarkers selected from Table 2C;

determining a sample expression score for the biomarker panel;

comparing the sample expression score to a threshold score; and

classifying the subject as responsive or non-responsive to the anti-angiogenic therapeutic agent based on whether the sample expression score is above or below the threshold expression score.

2. A method according to Claim 1, in which the biomarker panel comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM43A, CXCR2P1, MFAP2, MATN3, or RTP4.

3. A method according to Claim 1, in which the biomarker panel comprises the biomarkers listed in Table 2C.

4. A method according to any preceding claim, in which the sample expression score is determined by measuring an expression level for each biomarker and multiplying it by a corresponding weight, in which an expression signature defines the weight for each biomarker.

5. A method according to any preceding claim, in which the expression level of each biomarker in the biomarker panel is measured using a microarray, quantitative PCR, or an immunoassay.

6. A method according to any preceding claim, in which the sample comprises a tissue sample.

7. A method according to Claim 4, in which the expression signature is derived by a method comprising:

isolating total RNA from a sample set of diseased tissue;

hybridizing the isolated total RNA to a microarray to obtain a sample expression data set;

selecting those probes on the microarray with a variability above a defined significance threshold to form a preliminary biomarker set;

5 generating clusters of biomarkers within the preliminary biomarker set having a similar expression profile using a clustering algorithm;

identifying the biological processes or biological pathways for each cluster of biomarkers;

10 selecting the cluster corresponding to the biological process or biological pathway of interest; and

defining an expression signature by analyzing the expression levels of the biomarkers in the selected cluster in a the sample set of diseased tissue using a supervised or unsupervised training algorithm.

8. A method according to Claim 7, in which the expression signature is defined using a
15 PLS classifier, a SVM classifier, a SDA classifier, or a DSDA classifier.

9. A method according to any of Claims 6 to 8, in which the tissue is cancer tissue.

10. A method according to Claim 9, in which the cancer is ovarian cancer, prostate, breast cancer, colon cancer, or colorectal cancer.

11. A method according to any preceding claim, in which the anti-angiogenic therapeutic
20 agent is a VEGF-pathway-targeted therapeutic agent, an angiopoietin-TIE2 pathway inhibitor, an endogenous angiogenic inhibitor, or an immunomodulatory agent.

12. A method according to Claim 11, in which the VEGF pathway-targeted therapeutic agents include Bevacizumab (Avastin), Aflibercept (VEGF Trap), IMC-1121B (Ramucirumab), Imatinib (Gleevec), Sorafenib (Nexavar), Gefitinib (Iressa), Sunitinib
25 (Sutent), Erlotinib, Tivozinib, Cediranib (Recentin), Pazopanib (Votrient), BIBF 1120 (Vargatef), Dovitinib, Semaxanib (Sugen), Axitinib (AG013736), Vandetanib (Zactima), Nilotinib (Tasigna), Dasatinib (Sprycel), Vatalanib, Motesanib, ABT-869, TKI-258 or a combination thereof.

13. A method according to Claim 11, in which the angiopoietin-TIE2 pathway inhibitor includes AMG-386, PF-4856884 CVX-060, CEP-11981, CE-245677, MEDI-3617, CVX-241, Trastuzumab (Herceptin) or a combination thereof.

14. A method according to Claim 11, in which the endogenous angiogenic inhibitors include
5 Thombospondin, Endostatin, Tumstatin, Canstatin, Arrestin, Angiostatin, Vasostatin, Interferon alpha or a combination thereof.

15. A method according to Claim 11, in which the immunomodulatory agents include thalidomide and lenalidomide.

16. A method according to any preceding claim, further comprising determining the
10 subject's prognosis, in which a classification as responsive to the anti-angiogenic therapeutic agent indicates a good prognosis, the good prognosis indicating at least an increased expected survival time as compared to a classification as non-responsive to the anti-angiogenic therapeutic agent.

17. A method for predicting subject responsiveness to anti-angiogenic therapeutic agents
15 and providing treatment prognosis, the method comprising:

measuring expression levels of a first biomarker panel from a test sample of diseased tissue obtained from a subject with a disease or disorder, in which the biomarker panel comprises one or more biomarkers selected from Table 2C;

determining a first sample expression score for the first biomarker panel;

20 comparing the first sample expression score to a first threshold score

classifying the subject as having a good prognosis or bad prognosis based on whether the first sample expression score is above or below the first threshold score, in which a good prognosis indicates at least an increased expected survival time as compared to a bad prognosis and in which, in the event of a bad prognosis;

25 measuring expression levels of a second biomarker panel from the test sample of diseased tissue obtained from the subject, in which the second biomarker panel comprises one or more biomarkers selected from Table 2A or Table 2B;

determining a second sample expression score for the second biomarker panel;

comparing the second sample expression score to a second threshold score; and

classifying the subject as responsive or non-responsive to an anti-angiogenic therapeutic agent based on whether the second sample expression score is above or below the second threshold expression score.

18. A method according to Claim 17, in which the first biomarker panel comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4, and the second biomarker panel comprises one or more of CCDC80, INHBA, THBS2, SFRP2, MMP2, PLAU, FAP, FN1, COL8A1, and RAB31.

19. A method according to Claim 17, in which the first biomarker panel comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4, and the second biomarker panel comprises one or more of TMEM200A, GJB2, MMP13, GFPT2, POSTN, BICC1, CDH11, MRVI1, PMP22, and COL11A1.

20. A method according to Claim 17, in which the first biomarker panel consists of the biomarkers in Table 2C, and the second biomarker panel consists of the biomarkers in Table 2A or 2B.

21. A method according to any of Claims 16 to 20, in which the expression level of each biomarker in the biomarker panel is measured using a microarray, quantitative PCR, or an immunoassay.

22. A method for diagnosing a subject as having a cancer, or being susceptible to developing a cancer, that is responsive to an anti-angiogenic therapeutic, the method comprising;

measuring expression levels of a biomarker panel from a test sample obtained from a subject having or suspected of having a cancer that is responsive to an anti-angiogenic therapeutic, in which the biomarker panel comprises one or more biomarkers selected from Table 2C;

determining a sample expression score for the biomarker panel;

comparing the sample expression score to a threshold score; and

diagnosing the subject as having a cancer, or being susceptible to developing a cancer that is responsive to an anti-angiogenic therapeutic based on whether the sample expression score is above or below the threshold expression score.

23. A method according to Claim 22, in which the biomarker panel comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.

24. A method according to Claim 22, in which the biomarker panel comprises the
5 biomarkers listed in Table 2C.

25. A method according to any of Claims 22 to 24, in which the sample expression score is determined by measuring an expression level for each biomarker and multiplying it by a corresponding weight, in which an expression signature defines the weight for each biomarker.

10 26. A method according to Claim 25, in which the expression signature is defined using a PLS classifier, a SVM classifier, a SDA classifier, or a DSDA classifier.

27. A method according to any of Claims 22 to 26, in which the cancer is ovarian cancer, glioblastoma, breast cancer, prostate cancer, colorectal cancer or colon cancer.

15 28. A method according to any of Claims 22 to 27, in which the expression level of each biomarker in the biomarker panel is measured using a microarray, quantitative PCR, or an immunoassay.

29. Use of an anti-angiogenic therapeutic agent in the manufacture of a medicament for treating cancer in a subject, in which the subject is selected for treatment by:

20 measuring expression levels of a biomarker panel from a test sample obtained from the subject, in which the biomarker panel comprises one or more biomarkers selected from Table 2C;

determining a sample expression score for the biomarker panel;

comparing the sample expression score to a threshold score; and

in which:

25 (i) if the sample expression score is below the threshold score the subject is not selected for treatment; or

(ii) if the sample expression score is above the threshold score the subject is selected for treatment.

30. Use of an anti-angiogenic therapeutic agent in the manufacture of a medicament for treating cancer in a subject, in which the subject displays a sample expression score above a threshold score based on the expression levels of a biomarker panel comprising one or more biomarkers selected from Table 2C.

5 31. A method for selecting whether to administer an anti-angiogenic therapeutic agent to a subject, comprising:

measuring expression levels of a biomarker panel from a test sample obtained from the subject, in which the biomarker panel comprises one or more biomarkers selected from Table 2C;

10 determining a sample expression score for the biomarker panel;

comparing the sample expression score to a threshold score; and

in which:

(i) if the sample expression score is below the threshold score the subject is not selected for administration of an anti-angiogenic therapeutic agent; or

15 (ii) if the sample expression score is above the threshold score the subject is selected for administration of an anti-angiogenic therapeutic agent.

32. A use according to Claim 29 or 30 or a method method according to Claim 31, in which the biomarker panel comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.

20 33. A use according to 29 or 30 or a method method according to 31, in which the biomarker panel comprises the biomarkers listed in Table 2C.

34. A use or method according to any of Claims 29 to 33, in which the sample expression score is determined by measuring an expression level for each biomarker and multiplying it by a corresponding weight, in which an expression signature defines the weight for each
25 biomarker.

35. A use or method according to any of Claims 29 to 34, in which the expression level of each biomarker in the biomarker panel is measured using a microarray, quantitative PCR, or an immunoassay.

36. A use or method according to any of Claims 29 to 35, in which the sample comprises a tissue sample.

37. A use or method according to Claim 34, in which the expression signature is derived by a method comprising:

5 isolating total RNA from a sample set of diseased tissue;

hybridizing the isolated total RNA to a microarray to obtain a sample expression data set;

selecting those probes on the microarray with a variability above a defined significance threshold to form a preliminary biomarker set;

10 generating clusters of biomarkers within the preliminary biomarker set having a similar expression profile using a clustering algorithm;

identifying the biological processes or biological pathways for each cluster of biomarkers;

15 selecting the cluster corresponding to the biological process or biological pathway of interest; and

defining an expression signature by analyzing the expression levels of the biomarkers in the selected cluster in a the sample set of diseased tissue using a supervised or unsupervised training algorithm.

20 38. A use or method according Claim 37, in which the expression signature is defined using a PLS classifier, a SVM classifier, a SDA classifier, or a DSDA classifier.

39. A use or method according any of Claims 36 to 38, in which the tissue is cancer tissue.

40. A use or method according Claim 39, in which the cancer is ovarian cancer, prostate, breast cancer, colon cancer, or colorectal cancer.

25 41. A use or method according any of Claims 29 to 40, in which the anti-angiogenic therapeutic agent is a VEGF-pathway-targeted therapeutic agent, an angiopoietin-TIE2 pathway inhibitor, an endogenous angiogenic inhibitor, or an immunomodulatory agent.

42. A use or method according Claim 41, in which the VEGF pathway-targeted therapeutic agents include Bevacizumab (Avastin), Aflibercept (VEGF Trap), IMC-1121B

(Ramucirumab), Imatinib (Gleevec), Sorafenib (Nexavar), Gefitinib (Iressa), Sunitinib (Sutent), Erlotinib, Tivozinib, Cediranib (Recentin), Pazopanib (Votrient), BIBF 1120 (Vargatef), Dovitinib, Semaxanib (Sugen), Axitinib (AG013736), Vandetanib (Zactima), Nilotinib (Tasigna), Dasatinib (Sprycel), Vatalanib, Motesanib, ABT-869, TKI-258 or a combination thereof.

43. A use or method according Claim 41, in which the angiopoietin-TIE2 pathway inhibitor includes AMG-386, PF-4856884 CVX-060, CEP-11981, CE-245677, MEDI-3617, CVX-241, Trastuzumab (Herceptin) or a combination thereof.

44. A use or method according Claim 41, in which the endogenous angiogenic inhibitors include Thombospondin, Endostatin, Tumstatin, Canstatin, Arrestin, Angiostatin, Vasostatin, Interferon alpha or a combination thereof.

45. A use or method according Claim 41, in which the immunomodulatory agents include thalidomide and lenalidomide.

CLAIMS

1. A method for predicting a subject's responsiveness to an anti-angiogenic therapeutic agent comprising:

measuring expression levels of a biomarker panel from a test cancer sample obtained from a subject, in which the biomarker panel comprises IGF2 and at least one or more additional biomarkers selected from Table 2C;

determining a sample expression score for the biomarker panel;

comparing the sample expression score to a threshold score; and

classifying the subject as responsive or non-responsive to the anti-angiogenic therapeutic agent based on whether the sample expression score is above or below the threshold expression score.

2. A method according to Claim 1, in which the biomarker panel further comprises one or more of SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.

3. A method according to Claim 1, in which the biomarker panel comprises the biomarkers listed in Table 2C.

4. A method according to any preceding claim, in which the sample expression score is determined by measuring an expression level for each biomarker and multiplying it by a corresponding weight, in which an expression signature defines the weight for each biomarker.

5. A method according to any preceding claim, in which the expression level of each biomarker in the biomarker panel is measured using a microarray, quantitative PCR, or an immunoassay.

6. A method according to any preceding claim, in which the sample comprises a tissue sample.

7. A method according to Claim 4, in which the expression signature is derived by a method comprising:

isolating total RNA from a sample set of diseased tissue;

hybridizing the isolated total RNA to a microarray to obtain a sample expression data set;

selecting those probes on the microarray with a variability above a defined significance threshold to form a preliminary biomarker set;

5 generating clusters of biomarkers within the preliminary biomarker set having a similar expression profile using a clustering algorithm;

identifying the biological processes or biological pathways for each cluster of biomarkers;

10 selecting the cluster corresponding to the biological process or biological pathway of interest; and

defining an expression signature by analyzing the expression levels of the biomarkers in the selected cluster in a the sample set of diseased tissue using a supervised or unsupervised training algorithm.

8. A method according to Claim 7, in which the expression signature is defined using a
15 PLS classifier, a SVM classifier, a SDA classifier, or a DSDA classifier.

9. A method according to any preceding claim, in which the cancer is ovarian cancer, prostate, breast cancer, colon cancer, or colorectal cancer.

10. A method according to any preceding claim, in which the anti-angiogenic therapeutic agent is a VEGF-pathway-targeted therapeutic agent, an angiopoietin-TIE2 pathway inhibitor,
20 an endogenous angiogenic inhibitor, or an immunomodulatory agent.

11. A method according to Claim 10, in which the VEGF pathway-targeted therapeutic agents include Bevacizumab (Avastin), Afibercept (VEGF Trap), IMC-1121B (Ramucirumab), Imatinib (Gleevec), Sorafenib (Nexavar), Gefitinib (Iressa), Sunitinib (Sutent), Erlotinib, Tivozinib, Cediranib (Recentin), Pazopanib (Votrient), BIBF 1120
25 (Vargatef), Dovitinib, Semaxanib (Sugen), Axitinib (AG013736), Vandetanib (Zactima), Nilotinib (Tasigna), Dasatinib (Sprycel), Vatalanib, Motesanib, ABT-869, TKI-258 or a combination thereof.

12. A method according to Claim 10, in which the angiopoietin-TIE2 pathway inhibitor includes AMG-386, PF-4856884 CVX-060, CEP-11981, CE-245677, MEDI-3617, CVX-241, Trastuzumab (Herceptin) or a combination thereof.

13. A method according to Claim 10, in which the endogenous angiogenic inhibitors include
5 Thombospondin, Endostatin, Tumstatin, Canstatin, Arrestin, Angiostatin, Vasostatin, Interferon alpha or a combination thereof.

14. A method according to Claim 10, in which the immunomodulatory agents include thalidomide and lenalidomide.

15. A method according to any preceding claim, further comprising determining the
10 subject's prognosis, in which a classification as responsive to the anti-angiogenic therapeutic agent indicates a good prognosis, the good prognosis indicating at least an increased expected survival time as compared to a classification as non-responsive to the anti-angiogenic therapeutic agent.

16. A method for predicting subject responsiveness to anti-angiogenic therapeutic agents
15 and providing treatment prognosis, the method comprising:

measuring expression levels of a first biomarker panel from a test sample of cancer tissue obtained from a subject with cancer, in which the biomarker panel comprises IGF2 and at least one or more additional biomarkers selected from Table 2C;

determining a first sample expression score for the first biomarker panel;

20 comparing the first sample expression score to a first threshold score

classifying the subject as having a good prognosis or bad prognosis based on whether the first sample expression score is above or below the first threshold score, in which a good prognosis indicates at least an increased expected survival time as compared to a bad prognosis and in which, in the event of a bad prognosis;

25 measuring expression levels of a second biomarker panel from the test sample of diseased tissue obtained from the subject, in which the second biomarker panel comprises one or more biomarkers selected from Table 2A or Table 2B;

determining a second sample expression score for the second biomarker panel;

comparing the second sample expression score to a second threshold score; and

classifying the subject as responsive or non-responsive to an anti-angiogenic therapeutic agent based on whether the second sample expression score is above or below the second threshold expression score.

17. A method according to Claim 16, in which the first biomarker panel further comprises one or more of SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4, and the second biomarker panel comprises one or more of CCDC80, INHBA, THBS2, SFRP2, MMP2, PLAU, FAP, FN1, COL8A1, and RAB31.

18. A method according to Claim 16, in which the first biomarker panel further comprises one or more of SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4, and the second biomarker panel comprises one or more of TMEM200A, GJB2, MMP13, GFPT2, POSTN, BICC1, CDH11, MRVI1, PMP22, and COL11A1.

19. A method according to Claim 16, in which the first biomarker panel consists of the biomarkers in Table 2C, and the second biomarker panel consists of the biomarkers in Table 2A or 2B.

20. A method according to any of Claims 15 to 19, in which the expression level of each biomarker in the biomarker panel is measured using a microarray, quantitative PCR, or an immunoassay.

21. A method for diagnosing a subject as having a cancer, or being susceptible to developing a cancer, that is responsive to an anti-angiogenic therapeutic, the method comprising;

measuring expression levels of a biomarker panel from a test sample which is, or is suspected of being, cancerous obtained from a subject having or suspected of having a cancer that is responsive to an anti-angiogenic therapeutic, in which the biomarker panel comprises IGF2 and at least one or more additional biomarkers selected from Table 2C;

determining a sample expression score for the biomarker panel;

comparing the sample expression score to a threshold score; and

diagnosing the subject as having a cancer, or being susceptible to developing a cancer that is responsive to an anti-angiogenic therapeutic based on whether the sample expression score is above or below the threshold expression score.

22. A method according to Claim 21, in which the biomarker panel further comprises one or more of SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.
23. A method according to Claim 21, in which the biomarker panel comprises the
5 biomarkers listed in Table 2C.
24. A method according to any of Claims 21 to 23, in which the sample expression score is determined by measuring an expression level for each biomarker and multiplying it by a corresponding weight, in which an expression signature defines the weight for each biomarker.
- 10 25. A method according to Claim 24, in which the expression signature is defined using a PLS classifier, a SVM classifier, a SDA classifier, or a DSDA classifier.
26. A method according to any of Claims 21 to 25, in which the cancer is ovarian cancer, glioblastoma, breast cancer, prostate cancer, colorectal cancer or colon cancer.
- 15 27. A method according to any of Claims 21 to 26, in which the expression level of each biomarker in the biomarker panel is measured using a microarray, quantitative PCR, or an immunoassay.
28. Use of an anti-angiogenic therapeutic agent in the manufacture of a medicament for treating cancer in a subject, in which the subject is selected for treatment by:
- 20 measuring expression levels of a biomarker panel from a test cancer sample obtained from the subject, in which the biomarker panel comprises IGF2 and at least one or more additional biomarkers selected from Table 2C;
- determining a sample expression score for the biomarker panel;
- comparing the sample expression score to a threshold score; and
- in which:
- 25 (i) if the sample expression score is above the threshold score the subject is not selected for treatment; or
- (ii) if the sample expression score is below the threshold score the subject is selected for treatment.

29. Use of an anti-angiogenic therapeutic agent in the manufacture of a medicament for treating cancer in a subject, in which the subject displays a sample expression score below a threshold score based on the expression levels of a biomarker panel comprising IGF2 and at least one or more additional biomarkers selected from Table 2C.

5 30. A method for selecting whether to administer an anti-angiogenic therapeutic agent to a subject, comprising:

measuring expression levels of a biomarker panel from a test cancer sample obtained from the subject, in which the biomarker panel comprises IGF2 and at least one or more additional biomarkers selected from Table 2C;

10 determining a sample expression score for the biomarker panel;

comparing the sample expression score to a threshold score; and

in which:

(i) if the sample expression score is above the threshold score the subject is not selected for administration of an anti-angiogenic therapeutic agent; or

15 (ii) if the sample expression score is below the threshold score the subject is selected for administration of an anti-angiogenic therapeutic agent.

31. A use according to Claim 28 or 29 or a method according to Claim 30, in which the biomarker panel further comprises one or more of SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.

20 32. A use according to Claim 28 or 29 or a method according to Claim 30, in which the biomarker panel comprises the biomarkers listed in Table 2C.

33. A use or method according to any of Claims 28 to 32, in which the sample expression score is determined by measuring an expression level for each biomarker and multiplying it by a corresponding weight, in which an expression signature defines the weight for each

25 biomarker.

34. A use or method according to any of Claims 28 to 33, in which the expression level of each biomarker in the biomarker panel is measured using a microarray, quantitative PCR, or an immunoassay.

35. A use or method according to any of Claims 28 to 34, in which the sample comprises a tissue sample.

36. A use or method according to Claim 33, in which the expression signature is derived by a method comprising:

- 5 isolating total RNA from a sample set of diseased tissue;
- hybridizing the isolated total RNA to a microarray to obtain a sample expression data set;
- selecting those probes on the microarray with a variability above a defined significance threshold to form a preliminary biomarker set;
- 10 generating clusters of biomarkers within the preliminary biomarker set having a similar expression profile using a clustering algorithm;
- identifying the biological processes or biological pathways for each cluster of biomarkers;
- selecting the cluster corresponding to the biological process or biological pathway of interest; and
- 15 defining an expression signature by analyzing the expression levels of the biomarkers in the selected cluster in a the sample set of diseased tissue using a supervised or unsupervised training algorithm.

37. A use or method according Claim 33, in which the expression signature is defined using
20 a PLS classifier, a SVM classifier, a SDA classifier, or a DSDA classifier.

38. A use or method according any of Claims 28 to 37, in which the cancer is ovarian cancer, prostate, breast cancer, colon cancer, or colorectal cancer.

39. A use or method according any of Claims 28 to 38, in which the anti-angiogenic therapeutic agent is a VEGF-pathway-targeted therapeutic agent, an angiopoietin-TIE2
25 pathway inhibitor, an endogenous angiogenic inhibitor, or an immunomodulatory agent.

40. A use or method according Claim 39, in which the VEGF pathway-targeted therapeutic agents include Bevacizumab (Avastin), Afibercept (VEGF Trap), IMC-1121B (Ramucirumab), Imatinib (Gleevec), Sorafenib (Nexavar), Gefitinib (Iressa), Sunitinib (Sutent), Erlotinib, Tivozinib, Cediranib (Recentin), Pazopanib (Votrient), BIBF 1120

(Vargatef), Dovitinib, Semaxanib (Sugen), Axitinib (AG013736), Vandetanib (Zactima), Nilotinib (Tasigna), Dasatinib (Sprycel), Vatalanib, Motesanib, ABT-869, TKI-258 or a combination thereof.

41. A use or method according Claim 39, in which the angiopoietin-TIE2 pathway inhibitor
5 includes AMG-386, PF-4856884 CVX-060, CEP-11981, CE-245677, MEDI-3617, CVX-241, Trastuzumab (Herceptin) or a combination thereof.

42. A use or method according Claim 39, in which the endogenous angiogenic inhibitors include Thombospondin, Endostatin, Tumstatin, Canstatin, Arrestin, Angiostatin, Vasostatin, Interferon alpha or a combination thereof.

10 43. A use or method according Claim 39, in which the immunomodulatory agents include thalidomide and lenalidomide.