

Claims

1. A method for improving the overall survival of a patient suffering from a malignant disease or a disease involving physiological and pathological angiogenesis by treatment with an angiogenesis inhibitor, said method comprising the following steps:
 - (a) determining from a patient sample if the patient suffering from a malignant disease or a disease involving physiological and pathological angiogenesis has one or more variant alleles of the VEGFR-1 gene; and
 - (b) administering an angiogenesis inhibitor to the patient having one or more variant alleles of the VEGFR-1 gene.
2. A method for improving the progression-free survival of a patient suffering from a malignant disease or a disease involving physiological and pathological angiogenesis by treatment with an angiogenesis inhibitor, said method comprising the following steps:
 - (a) determining from a patient sample if the patient suffering from a malignant disease or a disease involving physiological and pathological angiogenesis has one or more variant alleles of the VEGFR-1 gene; and
 - (b) administering an angiogenesis inhibitor to the patient having one or more variant alleles of the VEGFR-1 gene.
3. An angiogenesis inhibitor for use in improving overall survival of a patient suffering from a malignant disease or a disease involving physiological and pathological angiogenesis wherein it is determined from a patient sample if the patient suffering from a malignant disease or a disease involving physiological and pathological angiogenesis has one or more variant alleles of the VEGFR-1 gene and whereby the angiogenesis inhibitor is to be administered to said patient having one or more variant alleles of the VEGFR-1 gene.
4. An angiogenesis inhibitor for use in improving progression-free survival of a patient suffering from a malignant disease or a disease involving physiological and pathological angiogenesis wherein it is determined from a patient sample if the patient suffering from a malignant disease or a disease involving physiological and pathological angiogenesis has one or more variant alleles of the VEGFR-1 gene and

whereby the angiogenesis inhibitor is to be administered to said patient having one or more variant alleles of the VEGFR-1 gene.

5. An in vitro method for the identification of a responder for or a patient sensitive to an angiogenesis inhibitor, said method comprising determining from a patient sample if a patient suffering from a malignant disease or a disease involving physiological and pathological angiogenesis has one or more variant alleles of the VEGFR-1 gene, whereby the presence of the one or more variant alleles of the VEGFR-1 gene is indicative for a responding patient or is indicative for a sensitivity of the patient to the angiogenesis inhibitor.
6. An angiogenesis inhibitor for use in an improved chemotherapy regimen for a patient suffering from a malignant disease or a disease involving physiological wherein it is determined from a patient sample if a patient suffering from said disease has one or more variant alleles of the VEGFR-1 gene in a patient sample and whereby the angiogenesis inhibitor is to be administered to the patient having one or more variant alleles of the VEGFR-1 gene.
7. The method or angiogenesis inhibitor of any one of 1 to 6, wherein the patient sample is a blood sample.
8. The method or angiogenesis inhibitor of any one of claims 1 to 7, wherein the patient sample is a peripheral blood sample.
9. The method or angiogenesis inhibitor of any one of claims 1 to 8, wherein the angiogenesis inhibitor is bevacizumab.
10. The method or angiogenesis inhibitor of any one of claims 1 to 9, wherein the angiogenesis inhibitor is administered as a co-treatment with a chemotherapeutic agent or chemotherapy regimen.
11. The method or angiogenesis inhibitor of any of claims 1 to 10, wherein the patient is being co-treated with one or more agents selected from the group consisting of interferon alpha, 5-fluorouracil, leucovorin, irinotecan, gemcitabine-erlotinib and platinum-based chemotherapeutic agents.

12. The method or angiogenesis inhibitor of claim 11, wherein the one or more platinum based chemotherapeutic agents is selected from the group consisting of paclitaxel, carboplatin and oxaliplatin.
13. The method or angiogenesis inhibitor of any of claims 1 to 12, wherein the malignant disease is pancreatic cancer, renal cell cancer, colorectal cancer, breast cancer, or lung cancer.
14. The method or angiogenesis inhibitor of any one of claims 1 to 12, wherein the malignant disease is pancreatic cancer.
15. The method or angiogenesis inhibitor of claim 14, wherein the angiogenesis inhibitor is bevacizumab and the co-therapy is gemcitabine-erlotinib therapy.
16. The method or angiogenesis inhibitor of any one of claims 2 and 4 to 11, wherein the malignant disease is renal cell cancer.
17. The method or angiogenesis inhibitor claim 16, wherein the angiogenesis inhibitor is bevacizumab and the co-therapy is interferon alpha therapy.
18. The method or angiogenesis inhibitor of any of claims 1 to 17, wherein the one or more variant alleles of the VEGFR-1 gene are in the region encompassing the tyrosine-kinase domain of the VEGFR-1 gene.
19. The method or angiogenesis inhibitor of any one of claims 1 to 18, wherein the one or more variant alleles of the VEGFR-1 gene are in the region encompassing exons 25 to 30 of the VEGFR-1 gene.
20. The method or angiogenesis inhibitor of any one of claims 1 to 19, wherein the one or more variant alleles of the VEGFR-1 gene are in an intron region of the VEGFR-1 gene.
21. The method or angiogenesis inhibitor of claim 13, 14 or 15, wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of rs9554316 (SEQ ID NO. 1), rs9582036 (SEQ ID NO. 2), rs9513070 (SEQ ID NO. 3) and rs9554320 (SEQ ID NO. 4).

22. The method or angiogenesis inhibitor of claim 16 or 17, wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of rs9554316 (SEQ ID NO. 1) and rs9513070 (SEQ ID NO. 3).
23. The method or angiogenesis inhibitor of claim 13, 14 or 15, wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of:
- (a) a sequence corresponding to rs9554316 (SEQ ID NO. 1) or having at least 80% homology to rs9554316 (SEQ ID NO. 1) having a substitution, deletion or addition of at least one nucleotide corresponding to position 51 of rs9554316 (SEQ ID NO. 1);
 - (b) a sequence corresponding to rs9582036 (SEQ ID NO. 2) or having at least 80% homology to rs9582036 (SEQ ID NO. 2) having a substitution, deletion or addition of at least one nucleotide corresponding to position 51 of rs9582036 (SEQ ID NO. 2);
 - (c) a sequence corresponding to rs9513070 (SEQ ID NO. 3) or having at least 80% homology to rs9513070 (SEQ ID NO. 3) having a substitution, deletion or addition of at least one nucleotide corresponding to position 51 of rs9513070 (SEQ ID NO. 3); and
 - (d) a sequence corresponding to rs9554320 (SEQ ID NO. 4) or having at least 80% homology to rs9554320 (SEQ ID NO. 4) having a substitution, deletion or addition of at least one nucleotide corresponding to position 51 of rs9554320 (SEQ ID NO. 4).
24. The method or angiogenesis inhibitor of claim 16 or 17, wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of:
- (a) a sequence corresponding to rs9554316 (SEQ ID NO. 1) or having at least 80% homology to rs9554316 (SEQ ID NO. 1) having a substitution, deletion or addition of at least one nucleotide corresponding to position 51 of rs9554316 (SEQ ID NO. 1); and
 - (b) a sequence corresponding to rs9513070 (SEQ ID NO. 3) or having at least 80% homology to rs9513070 (SEQ ID NO. 3) having a substitution, deletion or addition of at least one nucleotide corresponding to position 51 of rs9513070 (SEQ ID NO. 3).
25. The method or angiogenesis inhibitor of claim 13, 14 or 15, wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of:
- (a) a sequence corresponding to rs9554316 (SEQ ID NO. 1) or having at least 80% homology to rs9554316 (SEQ ID NO. 1), wherein position 51 is a T or G

- and having a substitution, deletion or addition of at least one nucleotide at any position from position 1 to 50 and 52 to 101;
- (b) a sequence corresponding to rs9582036 (SEQ ID NO. 2) or having at least 80% homology to rs9582036 (SEQ ID NO. 2) wherein position 51 is a C or A and having a substitution, deletion or addition of at least one nucleotide at any position from position 1 to 50 and 52 to 101;
 - (c) a sequence corresponding to rs9513070 (SEQ ID NO. 3) or having at least 80% homology to rs9513070 (SEQ ID NO. 3) wherein position 51 is a G or A and having a substitution, deletion or addition of at least one nucleotide at any position from position 1 to 50 and 52 to 101; and
 - (d) a sequence corresponding to rs9554320 (SEQ ID NO. 4) or having at least 80% homology to rs9554320 (SEQ ID NO. 4) wherein position 51 is a C or A and having a substitution, deletion or addition of at least one nucleotide at any position from position 1 to 50 and 52 to 101.
26. The method or angiogenesis inhibitor of claim 16 or 17, wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of:
- (a) a sequence corresponding to rs9554316 (SEQ ID NO. 1) or having at least 80% homology to rs9554316 (SEQ ID NO. 1), wherein position 51 is a T or G and having a substitution, deletion or addition of at least one nucleotide at any position from position 1 to 50 and 52 to 101; and
 - (b) a sequence corresponding to rs9513070 (SEQ ID NO. 3) or having at least 80% homology to rs9513070 (SEQ ID NO. 3) wherein position 51 is a G or A and having a substitution, deletion or addition of at least one nucleotide at any position from position 1 to 50 and 52 to 101.
27. The method or angiogenesis inhibitor of claim 13, 14 or 15, wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of rs9554316 (SEQ ID NO. 1), wherein position 51 is a G, rs9582036 (SEQ ID NO. 2), wherein position 51 is an A, rs9513070 (SEQ ID NO. 3), wherein position 51 is an A, and rs9554320 (SEQ ID NO. 4), wherein position 51 is a C.
28. The method or angiogenesis inhibitor of claim 16 or 17, wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of rs9554316 (SEQ ID NO. 1), wherein position 51 is a G, and rs9513070 (SEQ ID NO. 3), wherein position 51 is an A.

29. The method or angiogenesis inhibitor of claim 13, 14 or 15, wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of rs9554316 (SEQ ID NO. 1) and rs9582036 (SEQ ID NO. 2).
30. The method or angiogenesis inhibitor of claim 29, wherein wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of rs9554316 (SEQ ID NO. 1), wherein position 51 is a G, and rs9582036 (SEQ ID NO. 2), wherein position 51 is an A.
31. The method or angiogenesis inhibitor of any one of claims 1 to 17, wherein the wherein the one or more variant alleles of the VEGFR-1 gene are selected from the group consisting of rs17619037 (SEQ ID NO. 5), rs9579177 (SEQ ID NO. 6), rs9579176 (SEQ ID NO. 7), rs9554319 (SEQ ID NO. 8), rs7996030 (SEQ ID NO. 9), rs9513075 (SEQ ID NO. 10), rs7993418 (SEQ ID NO. 11), rs9513071 (SEQ ID NO. 12), rs12429309 (SEQ ID NO. 15), rs7982251 (SEQ ID NO. 16), rs9508016 (SEQ ID NO. 17), rs7982957 (SEQ ID NO. 18), rs3794400 (SEQ ID NO. 19), rs3794395 (SEQ ID NO. 52), rs9554317 (SEQ ID NO. 53), rs9513073 (SEQ ID NO. 54), rs9513074 (SEQ ID NO. 55), rs9508015 (SEQ ID NO. 56), rs2011950 (SEQ ID NO. 57), rs9513110 (SEQ ID NO. 58), rs9513112 (SEQ ID NO. 59), rs9513113 (SEQ ID NO. 60), rs9551471 (SEQ ID NO. 61), rs2296285 (SEQ ID NO. 62), rs9513116 (SEQ ID NO. 63), rs9551473 (SEQ ID NO. 64), rs7330109 (SEQ ID NO. 65), rs9508037 (SEQ ID NO. 66), rs1924981 (SEQ ID NO. 67), rs34140996 (SEQ ID NO. 68), rs7985584 (SEQ ID NO. 69), rs7992940 (SEQ ID NO. 70) and rs718273 (SEQ ID NO. 71).
32. The method or angiogenesis inhibitor of any one of claim 1 to 20 and 31, further comprising determining if the patient has one or more variant alleles selected from the group consisting of rs45455097 (SEQ ID NO. 40), rs1886233 (SEQ ID NO. 41), rs9554309 (SEQ ID NO. 42), rs11619230 (SEQ ID NO. 43), rs9554311 (SEQ ID NO. 44), rs11620238 (SEQ ID NO. 13), rs17618631 (SEQ ID NO. 14), rs4771233 (SEQ ID NO. 45), rs6491274 (SEQ ID NO. 46), rs7982639 (SEQ ID NO. 47), rs12877718 (SEQ ID NO. 48), rs10507382 (SEQ ID NO. 49), rs57354941 (SEQ ID NO. 50) and rs17086497 (SEQ ID NO. 51).
33. The method or angiogenesis inhibitor of any of claims 1 to 7, wherein the disease involving physiological and pathological angiogenesis is high grade glioma, glioblastoma, M. Rendu-Osler, von-Hippel-Lindau diseases, hemangiomas, psoriasis, Kaposi's sarcoma, ocular neovascularisation, rheumatoid arthritis, endometriosis,

atherosclerosis, myocardial ischemia, peripheral ischemia, cerebral ischemia or wound healing

34. Use of specific primers and/or probes for the preparation of a composition for predicting the response to or sensitivity to bevacizumab therapy of a patient suffering or suspected to suffer from metastatic pancreatic cancer wherein the primers and/or probes are capable of detecting at least one of the variant alleles selected from the group consisting of rs9554316 (SEQ ID NO. 1), SNPs rs9582036 (SEQ ID NO. 2), rs9513070 (SEQ ID NO. 3) and rs9554320 (SEQ ID NO. 4), whereby a G at position 51 of rs9554316 (SEQ ID NO. 1), an A at position 51 of SNPs rs9582036 (SEQ ID NO. 2), an A at position 51 of rs9513070 (SEQ ID NO. 3) and/or a C at position 51 of rs9554320 (SEQ ID NO. 4) is indicative of a patient response or sensitive to bevacizumab therapy.
35. Use of specific primers and/or probes for the preparation of a composition for predicting the response to or sensitivity to bevacizumab therapy of a patient suffering from or suspected to suffer from renal cell cancer wherein the primers and/or probes are capable of detecting at least one of the variant alleles are selected from the group consisting of at least one of the variant alleles selected from the group consisting of SNPs rs9554316 (SEQ ID NO. 1) and rs9513070 (SEQ ID NO. 3) whereby a G at position 51 of rs9554316 (SEQ ID NO. 1) and/or an A at position 51 of rs9513070 (SEQ ID NO. 3) is indicative of a patient response or sensitive to bevacizumab therapy.
36. A kit useful for carrying out the method, angiogenesis inhibitor or use of any of claims 1 to 35, comprising oligonucleotides or polynucleotides capable of determining the presence of at least one or more variant alleles of the VEGF-R1 gene.
37. Use of an oligonucleotides or polynucleotides for the detection of the one or more variant alleles of VEGFR-1 of the method, angiogenesis inhibitor or use of any one of claims 1 to 35.
38. The kit of claim 36 or use of claim 37, wherein said oligonucleotides or polynucleotides comprise primers and/or probes.
39. The kit of claim 38 or the use of claims 34, 35 or 38, wherein the primers are selected from the group consisting of SEQ ID NO. 20, SEQ ID NO. 25, SEQ ID NO. 30, SEQ ID NO. 35, SEQ ID NO. 21, SEQ ID NO. 26, SEQ ID NO. 31 and SEQ ID NO. 36.

40. The kit of claim 38 or the use of claim 34, 35 or 38, wherein the probes are selected from the group consisting of SEQ ID NO. 22, SEQ ID NO. 27, SEQ ID NO. 32 and SEQ ID NO. 37.
41. The kit of claim 38 or the use of any one of claims 34, 35 or 38, wherein the probes are selected from the group consisting of SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 38 and SEQ ID NO. 39.

CLAIMS

1. Bevacizumab for use in improving overall survival of a patient suffering from cancer wherein it is determined from a patient sample if the patient suffering from said cancer has the variant allele of the VEGFR-1 gene corresponding to rs9554316 (SEQ ID NO. 1), wherein position 51 is G, and whereby the bevacizumab is administered to said patient having said variant allele of the VEGFR-1 gene.
2. Bevacizumab for use in improving progression-free survival of a patient suffering from cancer wherein it is determined from a patient sample if the patient suffering from said cancer has the variant allele of the VEGFR-1 gene corresponding to rs9554316 (SEQ ID NO. 1), wherein position 51 is G, and whereby the bevacizumab is administered to said patient having said variant allele of the VEGFR-1 gene.
3. Bevacizumab for use in an improved chemotherapy regimen for a patient suffering from cancer wherein it is determined from a patient sample if a patient suffering from said cancer has the variant allele of the VEGFR-1 gene corresponding to rs9554316 (SEQ ID NO. 1), wherein position 51 is G, and whereby bevacizumab is administered to the patient having the variant allele of the VEGFR-1 gene.
4. The bevacizumab for use in a method according to any one of claims 1 to 3, wherein the patient sample is a blood sample.
5. The bevacizumab for use in a method according to any one of claims 1 to 4, wherein bevacizumab is administered as a co-treatment with a chemotherapeutic agent or chemotherapy regimen.
6. The bevacizumab for use in a method according to any one of claims 1 to 5, wherein the patient is being co-treated with one or more agents selected from the group consisting of interferon alpha, 5-fluorouracil, leucovorin, irinotecan, gemcitabine-erlotinib and platinum-based chemotherapeutic agents.
7. The bevacizumab for use in a method according to any one of claims 1 to 6, wherein the cancer is pancreatic cancer.
8. The bevacizumab for use in a method according to claim 7, wherein the patient is being co-treated with is gemcitabine-erlotinib therapy.

9. The bevacuzumab for use according to any one of claims 2 to 6, wherein the cancer is renal cell cancer.
10. The bevacizumab for use in a method according to claim 9, wherein the patient is being co-treated with interferon alpha therapy.
11. The bevacizumab for use in a method according to claim 7 or 8, further comprising determining if the patient has more variant alleles of the VEGFR-1 gene selected from the group consisting of:
 - (a) rs9582036 (SEQ ID NO. 2), wherein position 51 is A,
 - (b) rs9513070 (SEQ ID NO. 3), wherein position 51 is A; and
 - (c) rs9554320 (SEQ ID NO. 4), wherein position 51 is C.
12. The bevacizumab for use in a method according to claim 9 or 10, further comprising determining if the patient has the variant allele of the VEGFR-1 gene corresponding to rs9513070 (SEQ ID NO. 3), wherein position 51 is A.
13. Use of bevacizumab in the manufacture of a medicament for the improvement of overall survival of a patient suffering from cancer wherein it is determined from a patient sample if the patient suffering from said cancer has the variant allele of the VEGFR-1 gene corresponding to rs9554316 (SEQ ID NO. 1), wherein position 51 is G, and whereby the bevacizumab is administered to said patient having said variant allele of the VEGFR-1 gene.
14. Use of bevacizumab in the manufacture of a medicament for the improvement of progression-free survival of a patient suffering from cancer wherein it is determined from a patient sample if the patient suffering from said cancer has the variant allele of the VEGFR-1 gene corresponding to rs9554316 (SEQ ID NO. 1), wherein position 51 is G, and whereby the bevacizumab is administered to said patient having said variant allele of the VEGFR-1 gene.
15. Use of bevacizumab in the manufacture of a medicament in an improved chemotherapy regimen for a patient suffering from cancer wherein it is determined from a patient sample if a patient suffering from said cancer has the variant allele of the VEGFR-1 gene corresponding to rs9554316 (SEQ ID NO. 1), wherein position 51 is G, and whereby bevacizumab is administered to the patient having the variant allele of the VEGFR-1 gene.

16. The use according to any one of claims 13 to 15, wherein the patient sample is a blood sample.
17. The use according to any one of claims 13 to 16, wherein bevacizumab is administered as a co-treatment with a chemotherapeutic agent or chemotherapy regimen.
18. The use according to any one of claims 13 to 17, wherein the patient is being co-treated with one or more agents selected from the group consisting of interferon alpha, 5-fluorouracil, leucovorin, irinotecan, gemcitabine-erlotinib and platinum-based chemotherapeutic agents.
19. The use according to any one of claims 13 to 18, wherein the cancer is pancreatic cancer.
20. The use according to claim 19, wherein the patient is being co-treated with is gemcitabine-erlotinib therapy.
21. The use according to any one of claims 14 to 18, wherein the cancer is renal cell cancer.
22. The use according to claim 21, wherein the patient is being co-treated with interferon alpha therapy.
23. The use according to claim 19 or 20, wherein the patient sample is further determined for the presence of more variant alleles of the VEGFR-1 gene selected from the group consisting of:
 - (a) rs9582036 (SEQ ID NO. 2), wherein position 51 is A,
 - (b) rs9513070 (SEQ ID NO. 3), wherein position 51 is A; and
 - (c) rs9554320 (SEQ ID NO. 4), wherein position 51 is C.
24. The use according to claim 21 or 22, wherein the patient sample is further determined for the presence of the variant allele of the VEGFR-1 gene corresponding to rs9513070 (SEQ ID NO. 3), wherein position 51 is A.
25. An *in vitro* method for the identification of a responder for or a patient sensitive to bevacizumab, said method comprising determining from a patient sample if a patient suffering from cancer has the variant allele of the VEGFR-1 gene corresponding to rs9554316 (SEQ ID NO. 1), wherein position 51 is G, whereby the presence of said

allele of the VEGFR-1 gene is indicative for a responding patient or is indicative for a sensitivity of the patient to bevacizumab.

26. The *in vitro* method according to claim 25, wherein the patient sample is a blood sample.
27. The *in vitro* method according to claim 25 or 26, wherein the cancer is pancreatic cancer.
28. The *in vitro* method according to claim 25 or 26, wherein the cancer is renal cell cancer.
29. The *in vitro* method according to claim 27, further comprising determining if the patient has more variant alleles of the VEGFR-1 gene selected from the group consisting of:
 - (a) rs9582036 (SEQ ID NO. 2), wherein position 51 is A,
 - (b) rs9513070 (SEQ ID NO. 3), wherein position 51 is A; and
 - (c) rs9554320 (SEQ ID NO. 4), wherein position 51 is C.
30. The *in vitro* method according to claim 28, further comprising determining if the patient has the variant allele of the VEGFR-1 gene corresponding to rs9513070 (SEQ ID NO. 3), wherein position 51 is A.
31. Use of primers and/or probes for predicting the response to or sensitivity to bevacizumab therapy of a patient suffering or suspected to suffer from metastatic pancreatic cancer or renal cell cancer wherein the primers and/or probes are capable of detecting the variant allele of rs9554316 (SEQ ID NO. 1), whereby a G at position 51 of rs9554316 (SEQ ID NO. 1) is indicative of a patient response or sensitive to bevacizumab therapy.
32. Use of a kit for determining the patient sample according to any one of claims 1 to 30, comprising primers or probes capable of determining the presence of the variant allele of the VEGFR-1 gene corresponding to rs9554316 (SEQ ID NO. 1).
33. The use of claim 32, wherein
 - (a) the primers are selected from the group consisting of SEQ ID NO. 25 and SEQ ID NO. 26; or
 - (b) the probes is selected from the group consisting of SEQ ID NO. 27, SEQ ID NO. 28 or SEQ ID NO. 29.