

It has been described in WO 2011/015348 that one or more variant alleles of the VEGFR-1 gene are associated with improved outcome of the anti-angiogenesis treatment. Among the SNPs disclosed in WO 2011/015348 are rs9554316, rs9582036, rs9513070 and rs9554320, while other SNPs are identified by linkage disequilibrium and therefore linked to these four SNPs.

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Summary of the Invention

It has been found that one of the SNPs identified by linkage disequilibrium and disclosed in WO 2011/015348 is particularly useful as a predictive biomarker for the treatment outcome of an angiogenesis inhibitor, such as bevacizumab.

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The present ~~invention~~ disclosure therefore relates to a method of determining whether a patient is more or less suitably treated by a therapy with an angiogenesis inhibitor, such as bevacizumab, by determining the genotype at the synonymous T/C SNP located in exon 28 of VEGFR-1 corresponding respectively to TAT codon and TAC codon for tyrosine at position 1213. In one aspect, there is provided an in vitro method of determining whether a patient suffering from cancer or physiological or pathological angiogenic abnormalities is suitably treated by a therapy with an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab, said method comprising:

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(a) determining in a sample derived from a patient suffering from cancer or physiological or pathological angiogenic abnormalities the genotype at the synonymous T/C SNP located in exon 28 of VEGFR-1 corresponding respectively to TAT codon and TAC codon for tyrosine at position 1213, and

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(b) identifying said patient as more or less suitably treated by a therapy with an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab based on said genotype, wherein the presence of each T allele at said SNP indicates an increased likelihood that the patient is more suitably treated, or the presence of each C allele at said SNP indicates an increased likelihood that the patient is less suitably treated.

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The present ~~disclosure~~ invention also relates to a pharmaceutical composition comprising an angiogenesis inhibitor, such as bevacizumab, for the treatment of a patient suffering from cancer and having the genotype associated with an improved treatment effect at the synonymous T/C

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SNP located in exon 28 of VEGFR-1 corresponding respectively to TAT codon and TAC codon for tyrosine at position 1213. In another aspect, there is provided a pharmaceutical composition comprising an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab for the treatment of a patient suffering
5 from cancer or physiological or pathological angiogenic abnormalities, wherein the patient has been identified as more suitably treated with the angiogenesis inhibitor in accordance with the method as defined above.

The present ~~disclosure invention~~ further relates to a method for improving the treatment effect of
10 chemotherapy of a patient suffering from cancer by adding an angiogenesis inhibitor, such as bevacizumab, based on the genotype at the synonymous T/C SNP located in exon 28 of VEGFR-1 corresponding respectively to TAT codon and TAC codon for tyrosine at position 1213. In a further aspect, there is provided a method for improving the treatment effect of a chemotherapeutic agent or chemotherapy regimen of a patient suffering from cancer or
15 physiological or pathological angiogenic abnormalities by adding an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab, said method comprising:

(a) determining in a sample derived from a patient suffering from cancer or physiological or pathological angiogenic abnormalities the genotype at the synonymous T/C SNP located in exon
20 28 of VEGFR-1 corresponding respectively to TAT codon and TAC codon for tyrosine at position 1213;

(b) identifying said patient as more suitably treated by the addition of an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab based on said genotype, wherein the presence of each T allele at said SNP indicates
25 an increased likelihood that the patient is more suitably treated; and

(c) formulating said angiogenesis inhibitor in combination with a chemotherapeutic agent or chemotherapy regimen for administration to the patient identified as more suitably treated in accordance with (b).

30 In yet a further aspect, there is provided a kit for carrying out the method as defined above, comprising oligonucleotides capable of determining the genotype at the synonymous T/C SNP located in exon 28 of VEGFR-1 corresponding respectively to TAT codon and TAC codon for tyrosine at position 1213.

Detailed Description of the Embodiments

1. Definitions

- 5 The term "administering" means the administration of a pharmaceutical composition, such as an angiogenesis inhibitor, to the patient. For example, 2.5 mg/kg of body weight to 15 mg/kg of body weight bevacizumab (Avastin[®]) can be administered every week, every 2 weeks or every 3

Claims

1. An in vitro method of determining whether a patient suffering from cancer or physiological or pathological angiogenic abnormalities is suitably treated by a therapy with an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab, said method comprising:

(a) determining in a sample derived from a patient suffering from cancer or physiological or pathological angiogenic abnormalities the genotype at the synonymous T/C SNP located in exon 28 of VEGFR-1 corresponding respectively to TAT codon and TAC codon for tyrosine at position 1213, and

(b) identifying said patient as more or less suitably treated by a therapy with an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab based on said genotype, wherein the presence of each T allele at said SNP indicates an increased likelihood that the patient is more suitably treated, or the presence of each C allele at said SNP indicates an increased likelihood that the patient is less suitably treated.

2. The method of claim 1, wherein whether a patient is suitably treated by a therapy with an angiogenesis inhibitor is determined in terms of whether progression-free survival or overall survival is improved.

~~3. The method of any one of claims 1 to 2, wherein the method further comprises treating the patient by the therapy with an angiogenesis inhibitor.~~

~~43.~~ 43. The method of any one of claims 1 to ~~32~~ 43, wherein the angiogenesis inhibitor is formulated for administration ~~administered~~ as a co-treatment with a chemotherapeutic agent or chemotherapy regimen.

~~54.~~ 54. The method of any one of claims 1 to ~~43~~ 54, wherein the angiogenesis inhibitor is formulated for administration ~~administered~~ with one or more agents selected from the group consisting of taxanes, interferon alpha, 5-fluorouracil, capecitabine, leucovorin, gemcitabine, erlotinib and platinum-based chemotherapeutic agents.

~~65.~~ 65. The method of any one of claims 1 to ~~54~~ 65, wherein the cancer is pancreatic cancer, renal cell cancer, colorectal cancer, breast cancer or lung cancer.

76. A pharmaceutical composition comprising an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab for the treatment of a patient suffering from cancer or physiological or pathological angiogenic abnormalities, wherein the patient has been identified as more suitably treated with the angiogenesis inhibitor in accordance with the method of any one of claims 1 to 65.

87. A kit for carrying out the method of any one of claims 1 to 65, comprising oligonucleotides capable of determining the genotype at the synonymous T/C SNP located in exon 28 of VEGFR-1 corresponding respectively to TAT codon and TAC codon for tyrosine at position 1213.

98. A method for improving the treatment effect of a chemotherapeutic agent or chemotherapy regimen of a patient suffering from cancer or physiological or pathological angiogenic abnormalities by adding an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab, said method comprising:

(a) determining in a sample derived from a patient suffering from cancer or physiological or pathological angiogenic abnormalities the genotype at the synonymous T/C SNP located in exon 28 of VEGFR-1 corresponding respectively to TAT codon and TAC codon for tyrosine at position 1213;

(b) identifying said patient as more suitably treated by the addition of an angiogenesis inhibitor comprising bevacizumab or an antibody that binds essentially the same epitope on VEGF as bevacizumab based on said genotype, wherein the presence of each T allele at said SNP indicates an increased likelihood that the patient is more suitably treated; and

(c) ~~formulating administering~~ said angiogenesis inhibitor in combination with a chemotherapeutic agent or chemotherapy regimen for administration to the patient identified as more suitably treated in accordance with (b).

109. The method of claim 98, wherein whether a patient is suitably treated by a therapy with an angiogenesis inhibitor is determined in terms of whether progression-free survival or overall survival is improved.

~~11~~10. The method of any one of claims ~~9-8~~ to ~~10~~9, wherein the angiogenesis inhibitor is administered with one or more agents selected from the group consisting of taxanes, interferon alpha, 5-fluorouracil, capecitabine, leucovorin, gemcitabine, erlotinib and platinum-based chemotherapeutic agents.

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~~12~~11. The method of any one of claims ~~9-8~~ to ~~11~~10, wherein the cancer is pancreatic cancer, renal cell cancer, colorectal cancer, breast cancer or lung cancer.