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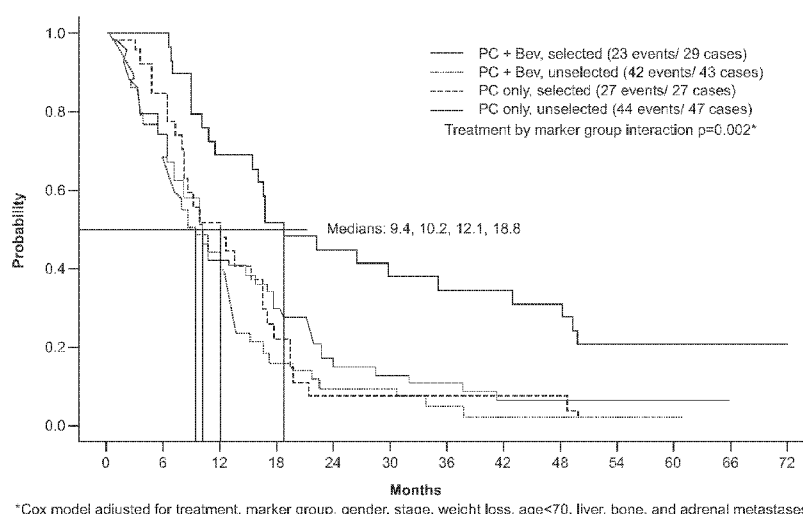


FIG. 6

(57) Abstract: The invention provides methods for determining the clinical outcomes for treatment with various treatment regimens available to cancer patients based on genotypes of the patients for genetic polymorphism markers. The invention also provides kits for making the determination.

GENETIC VARIANTS IN ANGIOGENESIS PATHWAY ASSOCIATED WITH CLINICAL OUTCOME

CROSS-REFERENCE TO RELATED APPLICATION

5 [0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional
Serial No. 61/172,674 filed April 24, 2009, the contents of which is incorporated by
reference in its entirety.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

10 [0002] This invention was made with government support under the National Institutes of
Health Grant SPECS 07000. Accordingly, the U.S. Government has certain rights to the
invention.

FIELD OF THE INVENTION

[0003] This invention relates to the field of pharmacogenomics and specifically to the
application of genetic polymorphisms to diagnose and treat diseases.

BACKGROUND OF THE INVENTION

15 [0004] In nature, organisms of the same species usually differ from each other in some
aspects, e.g., their appearance. The differences are genetically determined and are referred
to as polymorphism. Genetic polymorphism is the occurrence in a population of two or
more genetically determined alternative phenotypes due to different alleles. Polymorphism
20 can be observed at the level of the whole individual (phenotype), in variant forms of
proteins and blood group substances (biochemical polymorphism), morphological features
of chromosomes (chromosomal polymorphism) or at the level of DNA in differences of
nucleotides (DNA polymorphism).

25 [0005] Polymorphism also plays a role in determining differences in an individual's
response to drugs. Pharmacogenetics and pharmacogenomics are multidisciplinary research
efforts to study the relationship between genotype, gene expression profiles, and phenotype,
as expressed in variability between individuals in response to or toxicity from drugs.
Indeed, it is now known that cancer chemotherapy is limited by the predisposition of

specific populations to drug toxicity or poor drug response. For a review of the use of germline polymorphisms in clinical oncology, see Lenz (2004) J. Clin. Oncol. **22**(13):2519-2521; Park et al. (2006) Curr. Opin. Pharma. **6**(4):337-344; Zhang et al. (2006) Pharma. and Genomics **16**(7):475-483 and U.S. Patent Publ. No. 2006/0115827. For a review of
5 pharmacogenetics and pharmacogenomics in therapeutic antibody development for the treatment of cancer, see Yan and Beckman (2005) Biotechniques **39**:565-568.

[0006] The expression level of a variety of genes also have been linked to cancer prognosis and treatment protocol selection. Microarray gene expression profiling has been used to predict the prognosis of patients suffering from cancers including colon cancer,
10 breast cancer, lung cancer and lymphomas. Barrier et al. (2005) Oncogene **24**:6155-6164. Tumor tissue in these cancers have been shown to have both overexpression and underexpression of prognostic predictive genes. Furthermore, not only the tumor tissue itself can be predictive, but tumor-adjacent normal tissue has been show to predict tumor recurrence in patients suffering from rectal cancer treated with adjuvant chemoradiation.
15 Schneider et al. (2006) Pharmacogenetics and Genomics **16**(8):555-563. One recent study (Yang et al. (2006) Clinical Colorectal Cancer **6**(4):305-311) showed that gene expression levels of EGFR, Survivin and VEGF in tumor tissue were predictive markers for lymph node involvement in patients with locally advanced rectal cancer treated with surgical resection and adjuvant chemoradiation therapy.

20 [0007] Although considerable research correlating gene expression and/or polymorphisms has been reported, much work remains to be done. This invention supplements the existing body of knowledge and provides related advantages as well.

BRIEF SUMMARY OF THE INVENTION

[0008] The invention provides methods for determining the clinical outcomes for
25 treatment with various treatment regimens available to cancer patients based on genotypes of the patients for genetic polymorphism markers. The invention also provides kits for making the determination.

[0009] Thus, in one aspect, this invention also provides methods for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from
30 receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially

of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, GSTP1 A105G, or WNK1 rs11064560 T>G, wherein a genotype of:

- 5 a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (A/G or G/G) for GSTP1 A105G; or
- 10 f) (T/T or G/T) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a longer overall survival, or a genotype of:

- g) (C/T) for ICAM1 T469C;
- h) (C/C) for CXCR2 C+785T;
- i) (C/C) for ERCC1 3'UTR C>A;
- 15 j) (T/T) for KDR exon 11 T>A;
- k) (A/A) for GSTP1 A105G; or
- l) (G/G) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a shorter overall survival. Alternatively, a presence of none of a) to f) in the sample identifies the patient as likely to experience a shorter overall survival. In some embodiments, a patient having a genotype of a group that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than patients suffering from the cancer and receiving the therapy and having a genotype not in the group.

[0010] In another aspect, this invention provides methods for identifying a patient having a cancer likely to experience a longer or shorter overall survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A, wherein a genotype of:

- 30 a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
- b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or

c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A or A/T) for IL-8 T-251A,

identifies the patient as likely to experience a longer overall survival, or a genotype not in the group a), b) or c) identifies the patient as likely to experience a shorter overall survival.

5 In some embodiments, a patient having a genotype of a group that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than patients suffering from the cancer and receiving the therapy and not having a genotype of the group.

[0011] This invention also provides methods for predicting overall survival of a cancer
10 patient receiving an anti-VEGF-based therapy, comprising:

a) determining genotypes for at least two polymorphisms of the group ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A in a cell or tissue sample isolated from the patient; and

b) combining the genotypes using a suitable mathematical algorithm to predict
15 the length of overall survival of the patient.

[0012] This invention also provides methods for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for
20 at least two polymorphisms of the group VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C, wherein a genotype of:

a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or A/A) for ERCC1 3'UTR C>A; or

b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for
25 ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C,

identifies the patient as likely to experience a longer progression free survival, or a genotype not in the group a) or b) identifies the patient as likely to experience a shorter progression free survival. In some embodiments, a patient having a genotype of a group that is likely to experience a longer progression free survival is a patient that is likely to experience a

relatively longer progression free survival than patients suffering from the cancer and receiving the therapy and not having a genotype of the group.

[0013] This invention also provides methods for predicting progression free survival of a cancer patient receiving an anti-VEGF-based therapy, comprising:

- 5 a) determining genotypes for at least two polymorphisms of the group VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C in a cell or tissue sample isolated from the patient; and
- b) combining the genotypes using a suitable mathematical algorithm to predict the length of progression free survival of the patient.

10 **[0014]** This invention also provides methods for identifying a patient having a cancer that is likely to experience a longer progression free survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF G-
15 634C, VEGF C-1498T, CXCR2 C+785T, or WNK1 rs11064560 T>G, wherein a genotype of:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- 20 d) (C/C or T/T) for VEGF C-1498T
- e) (T/T or C/T) for CXCR2 C+785T; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a longer progression free survival, or a genotype of:

- 25 g) (C/C) for ERCC1 3'UTR C>A;
- h) (T/T) for KDR exon 11 T>A;
- i) (G/C) for VEGF G-634C;
- j) (C/T) for VEGF C-1498T
- k) (C/C) for CXCR2 C+785T; or
- 30 l) (G/G) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a shorter progression free survival.

Alternatively, a presence of none of a) to f) in the sample identifies the patient as likely to experience a shorter progression free survival. In some embodiments, a patient having a genotype of a group that is likely to experience a longer progression free survival is a

5 patient that is likely to experience a relatively longer progression free survival than patients suffering from the cancer and receiving the therapy and having a genotype not in the group.

[0015] This invention also provides methods for identifying a patient having a cancer that is more or less likely to respond to an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype
10 of a cell or tissue sample isolated from the patient for two polymorphisms of the group COX2 G-765C or WNK1 rs11064560 T>G, wherein a genotype of:

a) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G, identifies the patient as more likely to respond to the therapy, or a genotype that is not a) identifies the patient as less likely to respond to the therapy. In some embodiments, a
15 patient having a genotype that is more likely to respond to the therapy is a patient that is relatively more likely to respond to the therapy than patients suffering from the cancer and receiving the therapy and not having the genotype.

[0016] This invention also provides methods for identifying a patient having a cancer that is more or less likely to respond to an anti-VEGF-based therapy, comprising, or
20 alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for an ICAM1 T469C polymorphism, wherein a genotype of (C/C) for ICAM1 T469C identifies the patient as more likely to respond to the therapy, or a genotype of (T/T or C/T) for ICAM1 T469C identifies the patient as less likely to respond to the therapy. In some embodiments, a patient having a
25 genotype that is more likely to respond to the therapy is a patient that is relatively more likely to respond to the therapy than patients suffering from the cancer and receiving the therapy and not having the genotype.

[0017] In one aspect, the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of administration of an anti-VEGF antibody, a VEGF
30 inhibitor, or equivalents thereof. In one aspect, the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of, administration of

bevacizumab or an equivalent thereof. In another aspect, the anti-VEGF-based therapy further comprises, or alternatively consists essentially of, or yet further consists of, administration of a platinum drug. In one aspect, the platinum drug is carboplatin or an equivalent thereof. In another aspect, the anti-VEGF-based therapy further comprises, or
5 alternatively consists essentially of, or yet further consists of, administration of a mitotic inhibitor. In one aspect, the mitotic inhibitor is paclitaxel or an equivalent thereof.

[0018] In some embodiments, the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of administration of an anti-VEGF antibody in combination with a platinum drug and a mitotic inhibitor. In one aspect, the anti-VEGF-
10 based therapy comprises, or alternatively consists essentially of, or yet further consists of, administration of bevacizumab or an equivalent thereof in combination with carboplatin or an equivalent thereof, and paclitaxel or an equivalent thereof. In one aspect, the administration of the anti-VEGF antibody, the platinum drug or the mitotic inhibitor is concurrent or sequential.

[0019] This invention also provides methods for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group VEGF G-634C, IL-8
20 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A, wherein a genotype of:

- a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;
- b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G) for VEGF G-1154A; or
- c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or
25 A/A) for VEGF G-1154A,

identifies the patient as likely to experience a longer overall survival, or a genotype not in the group a), b) or c) identifies the patient as likely to experience a shorter overall survival. In one aspect, a patient having a genotype of a group that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival
30 than patients suffering from the cancer and receiving the therapy and not having a genotype of the group.

[0020] This invention also provides methods for predicting overall survival of a cancer patient receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of,

a) determining genotypes for at least two polymorphisms of the group VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A in a cell or tissue sample isolated from the patient; and

b) combining the genotypes using a suitable mathematical algorithm to predict the length of overall survival of the patient.

[0021] This invention also provides methods for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF C-1498T, VEGF G-1154A, EGF A+61G, or COX2 G-765C, wherein a genotype of:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (T/T or C/T) for VEGF C-1498T;
- f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

identifies the patient as likely to experience a longer overall survival, or a genotype of:

- h) (C/T) for ICAM1 T469C;
- i) (C/C) for CXCR2 C+785T;
- j) (C/C) for ERCC1 3'UTR C>A;
- k) (T/T) for KDR exon 11 T>A;
- l) (C/C) for VEGF C-1498T;
- m) (A/A) for VEGF G-1154A; or
- n) (G/G) for COX2 G-765C,

identifies the patient as likely to experience a shorter overall survival. Alternatively, a presence of none of a) to g) in the sample identifies the patient as likely to experience a shorter overall survival. In some embodiments, a patient having a genotype of a group that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than patients suffering from the cancer and receiving the therapy and having a genotype not in the group.

[0022] This invention also provides methods for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A, wherein a genotype of:

- a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11 T>A;
 - b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
 - c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,
- identifies the patient as likely to experience a longer progression free survival, or a genotype not in the group a) or b) identifies the patient as likely to experience a shorter progression free survival. In some embodiments, a patient having a genotype of a group that is likely to experience a longer progression free survival is a patient that is likely to experience a relatively longer progression free survival than patients suffering from the cancer and receiving the therapy and not having a genotype of the group.

[0023] This invention also provides methods for predicting progression free survival of a cancer patient receiving a platinum drug and mitotic inhibitor combination therapy, comprising:

- a) determining genotypes for at least two polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A in a cell or tissue sample isolated from the patient; and
- b) combining the genotypes using a suitable mathematical algorithm to predict the length of progression free survival of the patient.

[0024] In some embodiments of any of the methods the at least two polymorphisms comprise at least three, or alternatively at least three, or alternatively at least four polymorphisms of the group.

[0025] In some embodiments of any of the methods, the suitable mathematical algorithm is selected from the group: recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal component analysis. In one aspect, the suitable mathematical algorithm is recursive partitioning.

[0026] This invention also provides methods for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, EGF A+61G, and GSTP1 A105G, wherein a genotype of:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or A/G) for EGF A+61G; or
- d) (A/A or G/G) for GSTP1 A105G,

identifies the patient as likely to experience a longer progression free survival, or a genotype of:

- e) (C/C) for ERCC1 3'UTR C>A;
- f) (T/T) for KDR exon 11 T>A;
- g) (A/A) for EGF A+61G; or
- h) (A/G) for GSTP1 A105G,

identifies the patient as likely to experience a shorter progression free survival.

Alternatively, a presence of none of a) to d) in the sample identifies the patient as likely to experience a shorter progression free survival. In one aspect, a patient having a genotype of a group that is likely to experience a longer progression free survival is a patient that is likely to experience a relatively longer progression free survival than patients suffering from the cancer and receiving the therapy and having a genotype not in the group.

[0027] In one aspect, the platinum drug and mitotic inhibitor combination therapy comprises, or alternatively consists essentially of, or yet further consists of administration of

a platinum drug and a mitotic inhibitor. In some embodiments, the platinum drug is carboplatin or an equivalent thereof. In some embodiments, the mitotic inhibitor is paclitaxel or an equivalent thereof. In one aspect, the administration of the platinum drug and mitotic inhibitor is concurrent or sequential.

5 **[0028]** This invention further provides methods of identifying a patient having a cancer that is more likely to experience a side effect from a chemotherapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for a WNK1 rs110644560 G>T polymorphism, wherein a genotype of (T/T) for WNK1 rs110644560 G>T identifies the
10 patient as more likely to experience the side effect, or a genotype of (G/G or G/T) for WNK1 rs110644560 G>T identifies the patient as less likely to experience the side effect. In one aspect, a patient more likely to experience the side effect is a patient that is more likely to experience the side effect than patients having the cancer and receiving the therapy and having a genotype of (G/G or G/T) for WNK1 rs110644560 G>T. In another aspect, a
15 patient less likely to experience the side effect is a patient that is relatively less likely to experience the side effect than patients having the cancer and receiving the therapy and having a genotype of (T/T) for WNK1 rs110644560 G>T.

[0029] In one aspect, the chemotherapy is an anti-VEGF-based therapy or a platinum drug and mitotic inhibitor combination therapy. In another aspect, the chemotherapy comprises,
20 or alternatively consists essentially of, or yet further consists of, administration of carboplatin or an equivalent thereof in combination with paclitaxel or an equivalent thereof. In another aspect, the chemotherapy comprises, or alternatively consists essentially of, or yet further consists of, administration of bevacizumab or an equivalent thereof in combination with carboplatin or an equivalent thereof and paclitaxel or an equivalent
25 thereof.

[0030] In some embodiments of the this invention, the cancer patient is suffering from at least one cancer of the type of the group: metastatic or non-metastatic rectal cancer, metastatic or non-metastatic colon cancer, metastatic or non-metastatic colorectal cancer, non-small cell lung cancer (NSCLC), metastatic breast cancer, non-metastatic breast cancer,
30 renal cell carcinoma, glioblastoma multiforme, ovarian cancer, hormone-refractory prostate cancer, non-metastatic unresectable liver cancer, head and neck cancer, advanced Kaposi's sarcoma, or metastatic or unresectable locally advanced pancreatic cancer. In one aspect,

the cancer patient is suffering from lung cancer. In one aspect, the lung cancer is non-small cell lung cancer.

[0031] In some embodiments of the this invention, the sample comprises, or alternatively consists essentially of, or yet further consists of at least one of a tumor cell, a normal cell
5 adjacent to a tumor, a normal cell corresponding to the tumor tissue type, a blood cell, a peripheral blood lymphocyte, or combinations thereof.

[0032] In some embodiments of the this invention, the sample is at least one of a fixed tissue, a frozen tissue, a biopsy tissue, a resection tissue, a microdissected tissue, or combinations thereof.

10 [0033] This invention also provides a method for treating patients identified above as likely to responds to a therapy or have positive prognosis by administering to the patient an effective amount of the therapy identified as providing the benefit. A therapy or use of the therapy in for the preparation of a medicament to treat these patients are further provided herein.

15 [0034] This invention further provides kits for use in identifying a cancer patient for likely to experience a clinical outcome, comprising, or alternatively consisting essentially of, or yet further consisting of, one or more of suitable primers or probes or a microarray or panel, for screening one or more polymorphisms disclosed above, and instructions for use therein.

BRIEF DESCRIPTION OF THE THE FIGURES

20 [0035] **Figure 1** shows a recursive patitioning decision tree with polymorphisms for prediction of overall survival (OS) for patients treated with bevacizumab in combination with carboplatin/paclitaxel (BPC).

[0036] **Figure 2** shows a recursive patitioning decision tree with polymorphisms for prediction of progression free survival (PFS) for patients treated with bevacizumab in
25 combination with carboplatin/paclitaxel (BPC).

[0037] **Figure 3** shows a recursive patitioning decision tree with polymorphisms for prediction of overall survival (OS) for patients treated with carboplatin and paclitaxel (PC).

[0038] **Figure 4** shows a recursive partitioning decision tree with polymorphisms for prediction of progression free survival (PFS) for patients treated with carboplatin and paclitaxel (PC).

5 [0039] **Figure 5** shows a recursive partitioning decision tree with polymorphisms for prediction of response for patients treated with bevacizumab in combination with carboplatin/paclitaxel (BPC).

[0040] **Figure 6** shows KM curves by Selection Group and treatment arm, in addition to fitting a multivariable Cox model. This plot reflects OS classifying patients according to the SNPs that selected patients for superior OS (ICAM469 TT and VEGF634 GG,
10 ICAM469 $\neq$ TT and VEGF1498 $\neq$ CC and IL8251 $\neq$ TT).

[0041] **Figure 7** shows KM curves by Selection Group and treatment arm, in addition to fitting a multivariable Cox model. This plot reflects PFS classifying patients according to the SNPs that selected patients for superior PFS (ICAM469 TT and VEGF634 GG, ICAM469 $\neq$ TT and VEGF1498 $\neq$ CC and IL8251 $\neq$ TT).

15 [0042] **Figure 8** shows results of analysis to calculate PFS and response for individuals based on the OS Selection Criteria. The response rates (CR/PR) for each of the four groups: PCB selected (31%), PCB unselected (23%), PC selected (15%), PC unselected (11%). Fisher's test $p=0.13$.

[0043] **Figure 9** shows analysis to calculate OS and response for individuals based on the
20 PFS Selection Criteria. The response rates (CR/PR) for each of the four groups: PCB selected (44%), PCB unselected (16%), PC selected (10%), PC unselected (13%). Fisher's test $p=0.01$.

DETAILED DESCRIPTION OF THE INVENTION

[0044] Throughout this disclosure, various publications, patents and published patent
25 specifications are referenced by an identifying citation. The disclosures of these publications, patents and published patent specifications are hereby incorporated by reference into the present disclosure to more fully describe the state of the art to which this invention pertains.

[0045] The practice of the present invention employs, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature for example in the following publications. *See, e.g.*, Sambrook and Russell eds. MOLECULAR CLONING: A LABORATORY MANUAL, 3rd edition (2001); the series CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (F. M. Ausubel *et al.* eds. (2007)); the series METHODS IN ENZYMOLOGY (Academic Press, Inc., N.Y.); PCR 1: A PRACTICAL APPROACH (M. MacPherson *et al.* IRL Press at Oxford University Press (1991)); PCR 2: A PRACTICAL APPROACH (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)); ANTIBODIES, A LABORATORY MANUAL (Harlow and Lane eds. (1999)); CULTURE OF ANIMAL CELLS: A MANUAL OF BASIC TECHNIQUE (R.I. Freshney 5th edition (2005)); OLIGONUCLEOTIDE SYNTHESIS (M. J. Gait ed. (1984)); Mullis *et al.* U.S. Patent No. 4,683,195; NUCLEIC ACID HYBRIDIZATION (B. D. Hames & S. J. Higgins eds. (1984)); NUCLEIC ACID HYBRIDIZATION (M.L.M. Anderson (1999)); TRANSCRIPTION AND TRANSLATION (B. D. Hames & S. J. Higgins eds. (1984)); IMMOBILIZED CELLS AND ENZYMES (IRL Press (1986)); B. Perbal, A PRACTICAL GUIDE TO MOLECULAR CLONING (1984); GENE TRANSFER VECTORS FOR MAMMALIAN CELLS (J. H. Miller and M. P. Calos eds. (1987) Cold Spring Harbor Laboratory); GENE TRANSFER AND EXPRESSION IN MAMMALIAN CELLS (S.C. Makrides ed. (2003)) IMMUNOCHEMICAL METHODS IN CELL AND MOLECULAR BIOLOGY (Mayer and Walker, eds., Academic Press, London (1987)); WEIR'S HANDBOOK OF EXPERIMENTAL IMMUNOLOGY (L.A. Herzenberg *et al.* eds (1996)).

Definitions

[0046] As used herein, certain terms may have the following defined meanings. As used in the specification and claims, the singular form “a,” “an” and “the” include singular and plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes a single cell as well as a plurality of cells, including mixtures thereof.

[0047] As used herein, the term “comprising” is intended to mean that the compositions and methods include the recited elements, but not excluding others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of

any essential significance to the composition or method. "Consisting of" shall mean excluding more than trace elements of other ingredients for claimed compositions and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention. Accordingly, it is intended that the methods and compositions
5 can include additional steps and components (comprising) or alternatively including steps and compositions of no significance (consisting essentially of) or alternatively, intending only the stated method steps or compositions (consisting of).

[0048] All numerical designations, e.g., pH, temperature, time, concentration, and molecular weight, including ranges, are approximations which are varied (+) or (-) by
10 increments of 0.1. It is to be understood, although not always explicitly stated that all numerical designations are preceded by the term "about". The term "about" also includes the exact value "X" in addition to minor increments of "X" such as " $X + 0.1$ " or " $X - 0.1$." It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

15 **[0049]** The term "identify" or "identifying" is to associate or affiliate a patient closely to a group or population of patients who likely experience the same or a similar clinical response to treatment.

[0050] A "normal cell corresponding to the tumor tissue type" refers to a normal cell from a same tissue type as the tumor tissue. A non-limiting examples is a normal lung cell from a
20 patient having lung tumor, or a normal colon cell from a patient having colon tumor.

[0051] A "blood cell" refers to any of the cells contained in blood. A blood cell is also referred to as an erythrocyte or leukocyte, or a blood corpuscle. Non-limiting examples of blood cells include white blood cells, red blood cells, and platelets.

[0052] An anti-angiogenesis therapy refers to chemotherapy with an angiogenesis
25 inhibitor such as an anti-VEGF antibody or VEGF inhibitor, optionally with other chemotherapy agents. An angiogenesis inhibitor is a substance that inhibits angiogenesis (the growth of new blood vessels). It can be endogenous or come from outside as drug or a dietary component. The angiostatic agent endostatin and related chemicals can suppress the building of blood vessels, preventing the cancer from growing indefinitely. Other
30 angiostatic agents include, but are not limited to, bevacizumab, carboxyamidotriazole, TNP-

470, CM101, IFN- α , IL-12, platelet factor-4, suramin, SU5416, thrombospondin, VEGFR antagonists, angiostatic steroids + heparin, Cartilage-Derived Angiogenesis Inhibitory Factor, matrix metalloproteinase inhibitors, angiostatin, 2-methoxyestradiol, tecogalan, thrombospondin, prolactin, α V β 3 inhibitors, and linomide.

5 **[0053]** As used herein, “anti-VEGF therapy” intends treatment that targets the VEGF receptor family. Without being bound by theory, vascular endothelial growth factor (VEGF) ligands mediate their angiogenic effects by binding to specific VEGF receptors, leading to receptor dimerization and subsequent signal transduction. VEGF ligands bind to 3 primary receptors and 2 co-receptors. Of the primary receptors, VEGFR-1 and VEGFR-2
10 are mainly associated with angiogenesis. The third primary receptor, VEGFR-3, is associated with lymphangiogenesis.

[0054] In one aspect, anti-VEGF therapy comprises, or alternatively consists essentially of, or yet further, consists of an antibody or fragment thereof that binds the VEGF antigen. VEGF (Vascular endothelial growth factor) is a sub-family of growth factors (Entrez Gene:
15 7422, UniProtKB: P15692 <http://www.ncbi.nlm.nih.gov/> last accessed April 17, 2009), more specifically of platelet-derived growth factor family of cystine-knot growth factors. They are important signaling proteins involved in both vasculogenesis (the de novo formation of the embryonic circulatory system) and angiogenesis (the growth of blood vessels from pre-existing vasculature). A non-limiting example of such is the antibody sold
20 under the tradename bevacizumab (abbreviated “BV” herein) or equivalents thereof that bind to the same epitope. Equivalents can be polyclonal or monoclonal. The antibody may be of any appropriate species such as for example, murine, ovine or human. It can be humanized, recombinant, chimeric, recombinant, bispecific, a heteroantibody, a derivative or variant of a polyclonal or monoclonal antibody.

25 **[0055]** The term “antigen” is well understood in the art and includes substances which are immunogenic. VEGF is an example of an antigen.

[0056] An “anti-VEGF-based therapy” refers to chemotherapy with an anti-VEGF antibody or VEGF inhibitor, optionally with other chemotherapy agents.

[0057] Bevacizumab (BV) is sold under the trade name Avastin[®] by Genentech. It is a
30 humanized monoclonal antibody that binds to and inhibits the biologic activity of human

vascular endothelial growth factor (VEGF). Biological equivalent antibodies are identified herein as modified antibodies which bind to the same epitope of the antigen epitope such as ranibizumab sold under the tradename Lucentis, prevent the interaction of VEGF to its receptors (Flt01, KDR a.k.a. VEGFR2) and produce a substantially equivalent response, e.g., the blocking of endothelial cell proliferation and angiogenesis. Bevacizumab is also in the class of cancer drugs that inhibit angiogenesis (angiogenesis inhibitors).

[0058] “Platinum drugs” refer to any anticancer compound that includes platinum. In an embodiment, the anticancer drug can be selected from cisplatin (cDDP or cis-iamminedichloroplatinum(II)), carboplatin, oxaliplatin, and combinations thereof.

[0059] Carboplatin is a chemotherapy drug used against some forms of cancer (mainly ovarian carcinoma, lung, head and neck cancers). It was introduced in the late 1980s and has shown vastly reduced side-effects compared to its parent compound cisplatin. Cisplatin and carboplatin, as well as oxaliplatin or other platinum drugs, are classified as DNA alkylating agents. An equivalent of carboplatin includes, but are not limited to, cisplatin, oxaliplatin and other platinum drugs.

[0060] A “mitotic inhibitor” is a type of drug derived from natural substances such as plant alkaloids and primarily used in cancer treatment and certain types of cancer research including cytogenetics. Cancer cells are able to grow and eventually metastasize through continuous mitotic division. Generally speaking, mitotic inhibitors prevent cells from undergoing mitosis by disrupting microtubule polymerization, thus preventing cancerous growth. Mitotic inhibitors work by interfering with and halting mitosis (usually during the M phase of the cell cycle), so that the cell will no longer divide. Tubulin, a necessary protein for mitosis to occur, is suppressed by the mitotic inhibitor, preventing mitosis altogether. Examples of mitotic inhibitors frequently used in the treatment of cancer include paclitaxel, docetaxel, vinblastine, vincristine, and vinorelbine.

[0061] “Paclitaxel” is a mitotic inhibitor used in cancer chemotherapy. It was developed commercially by Bristol-Myers Squibb (BMS) and is sold under the trademark TAXOL[®]. In this formulation, paclitaxel is dissolved in Cremophor EL and ethanol, as a delivery agent. A newer formulation, in which paclitaxel is bound to albumin, is sold under the trademark Abraxane[®]. Paclitaxel stabilizes microtubules and as a result, interferes with the normal breakdown of microtubules during cell division. Together with docetaxel, it forms

the drug category of the taxanes. An equivalent of paclitaxel include, but are not limited to, docetaxel, vinblastine, vincristine, and vinorelbine.

[0062] The phrase “first line” or “second line” or “third line” refers to the order of treatment received by a patient. First line therapy regimens are treatments given first, whereas second or third line therapy are given after the first line therapy or after the second line therapy, respectively. The National Cancer Institute defines first line therapy as “the first treatment for a disease or condition. In patients with cancer, primary treatment can be surgery, chemotherapy, radiation therapy, or a combination of these therapies. First line therapy is also referred to those skilled in the art as “primary therapy” and “primary treatment.” See National Cancer Institute website as www.cancer.gov, last visited on May 1, 2008. Typically, a patient is given a subsequent chemotherapy regimen because the patient did not shown a positive clinical or sub-clinical response to the first line therapy or the first line therapy has stopped.

[0063] The term “adjuvant” chemotherapy refers to administration of a therapy or chemotherapeutic regimen to a patient after removal of a tumor by surgery. Adjuvant chemotherapy is typically given to minimize or prevent a possible cancer reoccurrence. Alternatively, “neoadjuvant” chemotherapy refers to administration of therapy or chemotherapeutic regimen before surgery, typically in an attempt to shrink the tumor prior to a surgical procedure to minimize the extent of tissue removed during the procedure.

[0064] In one aspect, the term “equivalent” or “biological equivalent” of an antibody means the ability of the antibody to selectively bind its epitope protein or fragment thereof as measured by ELISA or other suitable methods. Biologically equivalent antibodies include, but are not limited to, those antibodies, peptides, antibody fragments, antibody variant, antibody derivative and antibody mimetics that bind to the same epitope as the reference antibody. An example of an equivalent Bevacizumab antibody is one which binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF).

[0065] In one aspect, the term “equivalent” or “chemical equivalent” of a chemical means the ability of the chemical to selectively interact with its target protein, DNA, RNA or fragment thereof as measured by the inactivation of the target protein, incorporation of the chemical into the DNA or RNA or other suitable methods. Chemical equivalents include, but are not limited to, those agents with the same or similar biological activity and include,

without limitation a pharmaceutically acceptable salt or mixtures thereof that interact with and/or inactivate the same target protein, DNA, or RNA as the reference chemical.

[0066] The phrase “aggressive cancer treatment” refers to the cancer treatment, combination of treatments, or a chemotherapy regimen that is effective for treating the target cancer tumor or cell, but is associated with or known to cause higher toxicity, more side effects or is known in the art to be less efficacious than another type of treatment for the specified cancer type. One of skill in the art will be able to determine if a cancer treatment, combination of treatments, or chemotherapy regimen is less, more, or most aggressive. For example, a less aggressive treatment for a colon cancer patient may include adjuvant chemotherapy comprising surgical resection of the primary tumor and a chemotherapy regimen comprising 5-FU, leucovorin and bevacizumab. While a more aggressive cancer treatment may include adjuvant chemotherapy comprising surgical resection and a chemotherapy regimen comprising FOLFOX and BV, whereas the most aggressive cancer treatment may include surgical resection and a chemotherapy regime comprising Irinotecan and Cetuximab.

[0067] The term “allele,” which is used interchangeably herein with “allelic variant” refers to alternative forms of a gene or portions thereof. Alleles occupy the same locus or position on homologous chromosomes. When a subject has two identical alleles of a gene, the subject is said to be homozygous for the gene or allele. When a subject has two different alleles of a gene, the subject is said to be heterozygous for the gene. Alleles of a specific gene can differ from each other in a single nucleotide, or several nucleotides, and can include substitutions, deletions and insertions of nucleotides. An allele of a gene can also be a form of a gene containing a mutation.

[0068] The term “genotype” refers to the specific allelic composition of an entire cell or a certain gene and in some aspects a specific polymorphism associated with that gene, whereas the term “phenotype” refers to the detectable outward manifestations of a specific genotype.

[0069] As used herein, the term “determining the genotype of a cell or tissue sample” intends to identify the genotypes of polymorphic loci of interest in the cell or tissue sample. In one aspect, a polymorphic locus is a single nucleotide polymorphic (SNP) locus. If the allelic composition of a SNP locus is heterozygous, the genotype of the SNP locus will be

identified as “X/Y” wherein X and Y are two different nucleotides, e.g., C/T for the ICAM1 gene at position +469. If the allelic composition of a SNP locus is heterozygous, the genotype of the SNP locus will be identified as “X/X” wherein X identifies the nucleotide that is present at both alleles, e.g., C/C for ICAM1 gene at position +469. In
5 another aspect, a polymorphic locus harbors allelic variants of nucleotide sequences of different length. The genotype of the polymorphic locus will be identified with the length of the allelic variant, e.g., both alleles with < 20 CA repeats at intron 1 of the EGFR gene. The genotype of the cell or tissue sample will be identified as a combination of genotypes of all polymorphic loci of interest, e.g. C/C for ICAM1 gene at position +469 and both
10 alleles with < 20 CA repeats at intron 1 of the EGFR gene.

[0070] The terms “protein”, “polypeptide” and “peptide” are used interchangeably herein when referring to a gene product.

[0071] The term “genetic marker” refers to an allelic variant of a polymorphic region of a gene of interest and/or the expression level of a gene of interest.

15 **[0072]** The term “wild-type allele” refers to an allele of a gene which, when present in two copies in a subject results in a wild-type phenotype. There can be several different wild-type alleles of a specific gene, since certain nucleotide changes in a gene may not affect the phenotype of a subject having two copies of the gene with the nucleotide changes.

[0073] The term “polymorphism” refers to the coexistence of more than one form of a
20 gene or portion thereof. A portion of a gene of which there are at least two different forms, i.e., two different nucleotide sequences, is referred to as a “polymorphic region of a gene.” A polymorphic region can be a single nucleotide, the identity of which differs in different alleles.

[0074] A “polymorphic gene” refers to a gene having at least one polymorphic region.

25 **[0075]** The term “allelic variant of a polymorphic region of the gene of interest” refers to a region of the gene of interest having one of a plurality of nucleotide sequences found in that region of the gene in other individuals.

[0076] The term “genotype” refers to the specific allelic composition of an entire cell or a certain gene and in some aspects a specific polymorphism associated with that gene,

whereas the term “phenotype” refers to the detectable outward manifestations of a specific genotype.

[0077] “Cells,” “host cells” or “recombinant host cells” are terms used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0078] The phrase “amplification of polynucleotides” includes methods such as PCR, ligation amplification (or ligase chain reaction, LCR) and amplification methods. These methods are known and widely practiced in the art. See, e.g., U.S. Pat. Nos. 4,683,195 and 4,683,202 and Innis et al., 1990 (for PCR); and Wu, D.Y. et al. (1989) *Genomics* 4:560-569 (for LCR). In general, the PCR procedure describes a method of gene amplification which is comprised of (i) sequence-specific hybridization of primers to specific genes within a DNA sample (or library), (ii) subsequent amplification involving multiple rounds of annealing, elongation, and denaturation using a DNA polymerase, and (iii) screening the PCR products for a band of the correct size. The primers used are oligonucleotides of sufficient length and appropriate sequence to provide initiation of polymerization, i.e. each primer is specifically designed to be complementary to each strand of the genomic locus to be amplified.

[0079] Reagents and hardware for conducting PCR are commercially available. Primers useful to amplify sequences from a particular gene region are preferably complementary to, and hybridize specifically to sequences in the target region or in its flanking regions. Nucleic acid sequences generated by amplification may be sequenced directly. Alternatively the amplified sequence(s) may be cloned prior to sequence analysis. A method for the direct cloning and sequence analysis of enzymatically amplified genomic segments is known in the art.

[0080] The term “encode” as it is applied to polynucleotides refers to a polynucleotide which is said to “encode” a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for the polypeptide and/or a fragment thereof. The antisense strand is

the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

[0081] The term “isolated” as used herein refers to molecules or biological or cellular materials being substantially free from other materials. In one aspect, the term “isolated” refers to nucleic acid, such as DNA or RNA, or protein or polypeptide, or cell or cellular organelle, or tissue or organ, separated from other DNAs or RNAs, or proteins or polypeptides, or cells or cellular organelles, or tissues or organs, respectively, that are present in the natural source. The term “isolated” also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Moreover, an “isolated nucleic acid” is meant to include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. The term “isolated” is also used herein to refer to polypeptides which are isolated from other cellular proteins and is meant to encompass both purified and recombinant polypeptides. The term “isolated” is also used herein to refer to cells or tissues that are isolated from other cells or tissues and is meant to encompass both cultured and engineered cells or tissues.

[0082] When a genetic marker or polymorphism is used as a basis to identify a patient for a likely clinical outcome, the genetic marker or polymorphism is measured before and/or during treatment, and the values obtained are used by a clinician in assessing any of the following: (a) relatively probable or likely suitability of an individual to initially receive treatment(s); (b) relatively probable or likely unsuitability of an individual to initially receive treatment(s); (c) relatively likely responsiveness to treatment; (d) relatively probable or likely suitability of an individual to continue to receive treatment(s); (e) relatively probable or likely unsuitability of an individual to continue to receive treatment(s); (f) adjusting dosage; (g) predicting relative likelihood of clinical benefits; or (h) toxicity or side effects. As would be well understood by one in the art, measurement of the genetic marker or polymorphism in a clinical setting is a clear indication that this parameter was used as a basis for initiating, continuing, adjusting and/or ceasing administration of the treatments described herein.

[0083] The term “treating” as used herein is intended to encompass curing as well as ameliorating at least one symptom of the condition or disease. For example, in the case of

cancer, a response to treatment includes a reduction in cachexia, increase in survival time, elongation in time to tumor progression, reduction in tumor mass, reduction in tumor burden and/or a prolongation in time to tumor metastasis, time to tumor recurrence, tumor response, complete response, partial response, stable disease, progressive disease, progression free survival, overall survival, each as measured by standards set by the National Cancer Institute and the U.S. Food and Drug Administration for the approval of new drugs. See Johnson et al. (2003) J. Clin. Oncol. **21**(7):1404-1411.

[0084] As used herein, the term “patient” intends an animal, a mammal or yet further a human patient. For the purpose of illustration only, a mammal includes but is not limited to a simian, a murine, a bovine, an equine, a porcine or an ovine.

[0085] “An effective amount” intends to indicated the amount of a compound or agent administered or delivered to the patient which is most likely to result in the desired response to treatment. The amount is empirically determined by the patient’s clinical parameters including, but not limited to the stage of disease, age, gender, histology, and likelihood for tumor recurrence.

[0086] The term “clinical outcome”, “clinical parameter”, “clinical response”, or “clinical endpoint” refers to any clinical observation or measurement relating to a patient’s reaction to a therapy. Non-limiting examples of clinical outcomes include tumor response (TR), overall survival (OS), progression free survival (PFS), disease free survival, time to tumor recurrence (TTR), time to tumor progression (TTP), relative risk (RR), toxicity or side effect.

[0087] The term “likely to respond” intends to mean that the patient of a genotype is relatively more likely to experience a complete response or partial response than patients similarly situated without the genotype. Alternatively, the term “not likely to respond” intends to mean that the patient of a genotype is relatively less likely to experience a complete response or partial response than patients similarly situated without the genotype.

[0088] The term “suitable for a therapy” or “suitably treated with a therapy” shall mean that the patient is likely to exhibit one or more more desirable clinical outcome as compared to patients having the same disease and receiving the same therapy but possessing a different characteristic that is under consideration for the purpose of the comparison. In one

aspect, the characteristic under consideration is a genetic polymorphism or a somatic mutation. In another aspect, the characteristic under consideration is expression level of a gene or a polypeptide. In one aspect, a more desirable clinical outcome is relatively higher likelihood of or relatively better tumor response such as tumor load reduction. In another
5 aspect, a more desirable clinical outcome is relatively longer overall survival. In yet another aspect, a more desirable clinical outcome is relatively longer progression free survival or time to tumor progression. In yet another aspect, a more desirable clinical outcome is relatively longer disease free survival. In further another aspect, a more desirable clinical outcome is relative reduction or delay in tumor recurrence. In another
10 aspect, a more desirable clinical outcome is relatively decreased metastasis. In another aspect, a more desirable clinical outcome is relatively lower relative risk. In yet another aspect, a more desirable clinical outcome is relatively reduced toxicity or side effects. In some embodiments, more than one clinical outcomes are considered simultaneously. In one such aspect, a patient possessing a characteristic, such as a genotype of a genetic
15 polymorphism, may exhibit more than one more desirable clinical outcomes as compared to patients having the same disease and receiving the same therapy but not possessing the characteristic. As defined herein, the patients is considered suitable for the therapy. In another such aspect, a patient possessing a characteristic may exhibit one or more more desirable clinical outcome but simultaneously exhibit one or more less desirable clinical
20 outcome. The clinical outcomes will then be considered collectively, and a decision as to whether the patient is suitable for the therapy will be made accordingly, taking into account the patient's specific situation and the relevance of the clinical outcomes. In some embodiments, progression free survival or overall survival is weighted more heavily than tumor response in a collective decision making.

25 **[0089]** A "complete response" (CR) to a therapy defines patients with evaluable but non-measurable disease, whose tumor and all evidence of disease had disappeared.

[0090] A "partial response" (PR) to a therapy defines patients with anything less than complete response that were simply categorized as demonstrating partial response.

[0091] "Stable disease" (SD) indicates that the patient is stable.

30 **[0092]** "Progressive disease" (PD) indicates that the tumor has grown (i.e. become larger), spread (i.e. metastasized to another tissue or organ) or the overall cancer has gotten worse

following treatment. For example, tumor growth of more than 20 percent since the start of treatment typically indicates progressive disease. "Disease free survival" indicates the length of time after treatment of a cancer or tumor during which a patient survives with no signs of the cancer or tumor.

5 [0093] "Non-response" (NR) to a therapy defines patients whose tumor or evidence of disease has remained constant or has progressed.

[0094] "Overall Survival" (OS) intends a prolongation in life expectancy as compared to naïve or untreated individuals or patients.

10 [0095] "Progression free survival" (PFS) or "Time to Tumor Progression" (TTP) indicates the length of time during and after treatment that the cancer does not grow. Progression-free survival includes the amount of time patients have experienced a complete response or a partial response, as well as the amount of time patients have experienced stable disease.

[0096] "No Correlation" refers to a statistical analysis showing no relationship between the allelic variant of a polymorphic region or gene expression levels and clinical parameters.

15 [0097] "Tumor Recurrence" as used herein and as defined by the National Cancer Institute is cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumor or to another place in the body. It is also called recurrent cancer.

20 [0098] "Time to Tumor Recurrence" (TTR) is defined as the time from the date of diagnosis of the cancer to the date of first recurrence, death, or until last contact if the patient was free of any tumor recurrence at the time of last contact. If a patient had not recurred, then TTR was censored at the time of death or at the last follow-up.

25 [0099] "Relative Risk" (RR), in statistics and mathematical epidemiology, refers to the risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus a non-exposed group.

[0100] "Having the same cancer" is used when comparing one patient to another or alternatively, one patient population to another patient population. For example, the two patients or patient population will each have or be suffering from colon cancer.

[0101] As used herein, the terms “stage I cancer,” “stage II cancer,” “stage III cancer,” and “stage IV” refer to the TNM staging classification for cancer. Stage I cancer typically identifies that the primary tumor is limited to the organ of origin. Stage II intends that the primary tumor has spread into surrounding tissue and lymph nodes immediately draining the area of the tumor. Stage III intends that the primary tumor is large, with fixation to deeper structures. Stage IV intends that the primary tumor is large, with fixation to deeper structures. See pages 20 and 21, CANCER BIOLOGY, 2nd Ed., Oxford University Press (1987).

[0102] A “tumor” is an abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells and serving no physiological function. A “tumor” is also known as a neoplasm.

[0103] A “lymph node” refers to a rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue, which filter lymphatic fluid and stores white blood cells. Cancers described herein can spread to the lymphatic system and this spreading is used, in part, to determine the cancer stage. For example, if a cancer is “lymph node negative,” the cancer has not spread to the surrounding or nearby lymph nodes and thus the lymphatic system. Conversely, if the cancer has spread to the surrounding or nearby lymph nodes, the cancer is “lymph node positive.”

[0104] The term “blood” refers to blood which includes all components of blood circulating in a subject including, but not limited to, red blood cells, white blood cells, plasma, clotting factors, small proteins, platelets and/or cryoprecipitate. This is typically the type of blood which is donated when a human patient gives blood.

[0105] As used herein, an “antibody” includes whole antibodies and any antigen binding fragment or a single chain thereof. Thus the term “antibody” includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule. Examples of such include, but are not limited to a complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework (FR) region, or any portion thereof, or at least one portion of a binding protein, any of which can be incorporated into an antibody of the present invention.

[0106] If an antibody is used in combination with the above-noted chemotherapy or for diagnosis or as an alternative to the chemotherapy, the antibodies can be polyclonal or monoclonal and can be isolated from any suitable biological source, e.g., murine, rat, sheep and canine. Additional sources are identified infra.

5 **[0107]** The term “antibody” is further intended to encompass digestion fragments, specified portions, derivatives and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Examples of binding fragments encompassed within the term “antigen binding
10 portion” of an antibody include a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH₁ domains; a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH₁ domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, a dAb fragment (Ward et al. (1989) *Nature* **341**:544-546), which consists of
15 a VH domain; and an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv)). Bird et al. (1988) *Science* **242**:423-426 and
20 Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* **85**:5879-5883. Single chain antibodies are also intended to be encompassed within the term “fragment of an antibody.” Any of the above-noted antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for binding specificity and neutralization activity in the same manner as are intact antibodies.

25 **[0108]** The term “epitope” means a protein determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and nonconformational epitopes are distinguished in that the binding to the former but not the
30 latter is lost in the presence of denaturing solvents.

[0109] The term “antibody variant” is intended to include antibodies produced in a species other than a mouse. It also includes antibodies containing post-translational modifications

to the linear polypeptide sequence of the antibody or fragment. It further encompasses fully human antibodies.

[0110] The term “antibody derivative” is intended to encompass molecules that bind an epitope as defined above and which are modifications or derivatives of a native monoclonal antibody of this invention. Derivatives include, but are not limited to, for example, bispecific, multispecific, heterospecific, trispecific, tetraspecific, multispecific antibodies, diabodies, chimeric, recombinant and humanized.

[0111] The term “bispecific molecule” is intended to include any agent, e.g., a protein, peptide, or protein or peptide complex, which has two different binding specificities. The term “multispecific molecule” or “heterospecific molecule” is intended to include any agent, e.g. a protein, peptide, or protein or peptide complex, which has more than two different binding specificities.

[0112] The term “heteroantibodies” refers to two or more antibodies, antibody binding fragments (e.g., Fab), derivatives thereof, or antigen binding regions linked together, at least two of which have different specificities.

[0113] The term “human antibody” as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term “human antibody” as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. Thus, as used herein, the term “human antibody” refers to an antibody in which substantially every part of the protein (e.g., CDR, framework, C_L, C_H domains (e.g., C_{H1}, C_{H2}, C_{H3}), hinge, (VL, VH)) is substantially non-immunogenic in humans, with only minor sequence changes or variations. Similarly, antibodies designated primate (monkey, baboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pig, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, family specific antibodies. Further, chimeric antibodies include any combination of the above. Such changes or variations optionally and preferably retain or reduce the immunogenicity in humans or other species relative to non-modified

antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when a human antibody is a single chain antibody, it can comprise a linker peptide that is not found in native human antibodies. For example, an Fv can comprise a linker peptide, such as two to about eight glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

[0114] As used herein, a human antibody is “derived from” a particular germline sequence if the antibody is obtained from a system using human immunoglobulin sequences, e.g., by immunizing a transgenic mouse carrying human immunoglobulin genes or by screening a human immunoglobulin gene library. A human antibody that is “derived from” a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino acid sequence of human germline immunoglobulins. A selected human antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the human antibody as being human when compared to the germline immunoglobulin amino acid sequences of other species (e.g., murine germline sequences). In certain cases, a human antibody may be at least 95%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a human antibody derived from a particular human germline sequence will display no more than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene. In certain cases, the human antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

[0115] The terms “monoclonal antibody” or “monoclonal antibody composition” as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

[0116] A “human monoclonal antibody” refers to antibodies displaying a single binding specificity which have variable and constant regions derived from human germline immunoglobulin sequences.

[0117] The term “recombinant human antibody”, as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, antibodies isolated from a host cell transformed to express the antibody, e.g., from a transfectoma, antibodies isolated from a recombinant, combinatorial human antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0118] As used herein, “isotype” refers to the antibody class (e.g., IgM or IgG1) that is encoded by heavy chain constant region genes.

[0119] The term “hazard ratio” is a survival analysis in the effect of an explanatory variable on the hazard or risk of an event. In another aspect, “hazard ratio” is an estimate of relative risk, which is the risk of an event or development of a disease relative to treatment and in some aspects the expression levels of the gene of interest. Statistical methods for determining hazard ratio are well known in the art.

[0120] “Multivariate analysis” or “multivariate statistics” refers to a collection of mathematical or statistical procedures which involve observation and analysis of more than one variable at a time. “Multivariate” refers to having or involving a number of independent mathematical or statistical variables. In one aspect, a multivariate analysis is a bivariate analysis.

[0121] A “mathematical algorithm” for a multivariate analysis refers to a mathematical or statistical algorithm that analyze more than one variable at a time. In one aspect, a mathematical algorithm makes a classification or prediction from the analysis. In some embodiments, a mathematical algorithm refers to a machine learning approach. In some
5 embodiments, a mathematical algorithm refers to a statistical pattern recognition approach. Non-limiting examples of mathematical algorithms include clustering systems, Hotelling’s T-square, multivariate analysis of variance (MANOVA), discriminant analysis, principal component analysis, redundancy analysis, correspondence analysis, linear discriminant analysis, quadratic discriminant analysis, logistic regression, regression tree, artificial neural
10 networks, multidimensional scaling, multidimensional histogram, canonical correlation analysis, random forest, nearest neighbor, support vector machine, decision tree, and recursive partitioning.

[0122] A “suitable mathematical algorithm” for a multivariate analysis refers to a mathematical or statistical algorithm suitable for analyzing the type of data obtained. It is
15 known in the art that each algorithm has strength with regard to certain data types and sample size. Therefore, selection of suitable mathematical algorithms can be based on data types or sample sizes. Additionally, a suitable mathematical algorithm can be experimentally determined by comparing multiple algorithms with experimental data. For example, when the data are categorical such as genetic polymorphic data, suitable
20 mathematical algorithms include, but are not limited to, recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal component analysis. In another example, the data are numerical or continuous such as gene expression values, suitable mathematical algorithms include, but are not limited discriminant analysis, principal component analysis, linear discriminant analysis,
25 quadratic discriminant analysis, artificial neural networks, multidimensional scaling, multidimensional histogram, random forest, nearest neighbor, support vector machine, decision tree, and recursive partitioning.

[0123] “Recursive partitioning” is a statistical method for multivariable analysis. Recursive partitioning creates a decision tree that strives to correctly classify members of
30 the population based on several dichotomous dependent variables. A decision tree (or tree diagram) is a decision support tool that uses a tree-like graph or model of decisions and their possible consequences, including chance event outcomes, resource costs, and utility.

In data mining and machine learning, a decision tree is a predictive model; that is, a mapping from observations about an item to conclusions about its target value. More descriptive names for such tree models are classification tree (discrete outcome) or regression tree (continuous outcome). In these tree structures, leaves represent
5 classifications and branches represent conjunctions of features that lead to those classifications. Details of the recursive partitioning algorithm can be found in, e.g., Yuan and Shaw (1995) "Induction of fuzzy decision trees," Fuzzy Sets and Systems, 69(2):125-139, which is incorporated by reference in its entirety in the present application.

Descriptive Embodiments

10 **[0124]** The invention further provides diagnostic, prognostic and therapeutic methods, which are based, at least in part, on determination of a genetic polymorphism in a gene of interest identified herein.

[0125] For example, information obtained using the diagnostic assays described herein is useful for determining if a subject is suitable for cancer treatment of a given type or is likely
15 to experience an extended survival time or side effect. Based on the prognostic information, a doctor can recommend a therapeutic protocol, useful for reducing the malignant mass or tumor in the patient or treat cancer in the individual.

[0126] It is to be understood that information obtained using the diagnostic assays described herein may be used alone or in combination with other information, such as, but
20 not limited to, genotypes or expression levels of other genes, clinical chemical parameters, histopathological parameters, or age, gender and weight of the subject. When used alone, the information obtained using the diagnostic assays described herein is useful in determining or identifying the clinical outcome of a treatment, likely side effects, selecting a patient for a treatment, or treating a patient, etc. When used in combination with other
25 information, on the other hand, the information obtained using the diagnostic assays described herein is useful in aiding in the determination or identification of clinical outcome of a treatment, aiding in the selection of a patient for a treatment, or aiding in the treatment of a patient and etc. In a particular aspect, the identity of a polymorphism at a position within a gene of interest is used in a panel of genes, each of which contributes to the final
30 diagnosis, prognosis or treatment.

[0127] The methods of this invention are useful for the diagnosis, prognosis and treatment of patients suffering from at least one or more cancer of the group: metastatic or non-metastatic rectal cancer, metastatic or non-metastatic colon cancer, metastatic or non-metastatic colorectal cancer, non-small cell lung cancer (NSCLC), metastatic breast cancer, non-metastatic breast cancer, renal cell carcinoma, glioblastoma multiforme, ovarian cancer, hormone-refractory prostate cancer, non-metastatic unresectable liver cancer, head and neck cancer, advanced Kaposi's sarcoma, or metastatic or unresectable locally advanced pancreatic cancer.

[0128] The methods are useful in the assistance of an animal, a mammal or yet further a human patient. For the purpose of illustration only, a mammal includes but is not limited to a human patient, a simian, a murine, a bovine, an equine, a porcine or an ovine.

Descriptive Embodiments

[0129] Provided is a method for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, GSTP1 A105G, or WNK1 rs11064560 T>G, wherein a genotype of:

- a) (T/T or C/C) for ICAM1 T469C;
 - b) (C/T or T/T) for CXCR2 C+785T;
 - c) (A/C or A/A) for ERCC1 3'UTR C>A;
 - d) (A/T or A/A) for KDR exon 11 T>A;
 - e) (A/G or G/G) for GSTP1 A105G; or
 - f) (T/T or G/T) for WNK1 rs11064560 T>G,
- identifies the patient as likely to experience a longer overall survival, or a genotype of:
- g) (C/T) for ICAM1 T469C;
 - h) (C/C) for CXCR2 C+785T;
 - i) (C/C) for ERCC1 3'UTR C>A;
 - j) (T/T) for KDR exon 11 T>A;
 - k) (A/A) for GSTP1 A105G; or
 - l) (G/G) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a shorter overall survival. Alternatively, the presence of none of a) to f) identifies the patient as likely to experience a shorter overall survival.

[0130] In one aspect, a genotype of:

- 5 a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (A/G or G/G) for GSTP1 A105G; or
- 10 f) (T/T or G/T) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a longer overall survival.

[0131] As used above, in some embodiments, a patient having a genotype of a group that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than patients suffering from the cancer and receiving the
15 therapy and having a genotype not in the group.

[0132] Also provided is a method for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least two
20 polymorphisms of the group ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A, wherein a genotype of:

- a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
- b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or
- c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A
25 or A/T) for IL-8 T-251A,

identifies the patient as likely to experience a longer overall survival, or a genotype not in the group a), b) or c) identifies the patient as likely to experience a shorter overall survival.

[0133] In one aspect, the at least two polymorphisms comprise ICAM1 T469C and VEGF G-534C and wherein the genotype of a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-
30 634C identifies the patient as likely to experience a longer overall survival.

[0134] In one aspect of each of the above methods, a patient having a genotype of a group that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than patients suffering from the cancer and receiving the therapy and not having a genotype of the group.

5 [0135] Also provided is a method for predicting overall survival of a cancer patient receiving an anti-VEGF-based therapy, comprising:

a) determining genotypes for at least two polymorphisms of the group ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A in a cell or tissue sample isolated from the patient; and

10 b) combining the genotypes using a suitable mathematical algorithm to predict the length of overall survival of the patient.

[0136] In one aspect, the at least two polymorphisms comprise at least three polymorphisms of the group. In some embodiments, a multivariate analysis does not require data from all variables. Accordingly, in one aspect, the at least two polymorphism
15 may comprise two polymorphisms, or alternatively three polymorphisms, or alternatively four polymorphisms.

[0137] In one aspect, the at least two polymorphisms include at least ICAM1 T469C. In another aspect, the at least two polymorphisms comprise ICAM1 T469C and VEGF G-634C.

20 [0138] In one aspect, the suitable mathematical algorithm of step b) is selected from the group: recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal component analysis. In one aspect, the suitable mathematical algorithm of step b) is recursive partitioning.

[0139] Also provided is a method for identifying a patient having a cancer that is likely to
25 experience a longer or shorter progression free survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C, wherein a genotype of:

a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or A/A) for ERCC1 3'UTR C>A; or

b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C,

5 identifies the patient as likely to experience a longer progression free survival, or a genotype not in the group a) or b) identifies the patient as likely to experience a shorter progression free survival.

[0140] In one aspect, the at least two polymorphisms comprise VEGF G-634C, CXCR2 C+785T, and ERCC1 3'UTR C>A and wherein the genotype of a) (G/G) for VEGF G-
10 634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or A/A) for ERCC1 3'UTR C>A identifies the patient as likely to experience a longer progression free survival.

In one aspect of each of the above methods, a patient having a genotype of a group that is likely to experience a longer progression free survival is a patient that is likely to experience a relatively longer progression free survival than patients suffering from the cancer and
15 receiving the therapy and not having a genotype of the group.

[0141] Also provided is a method for predicting progression free survival of a cancer patient receiving an anti-VEGF-based therapy, comprising:

a) determining genotypes for at least two polymorphisms of the group VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C in a
20 cell or tissue sample isolated from the patient; and

b) combining the genotypes using a suitable mathematical algorithm to predict the length of progression free survival of the patient.

[0142] In one aspect, the at least two polymorphisms comprise at least three polymorphisms of the group. In another aspect, the at least two polymorphisms comprise at
25 least four polymorphisms of the group. In some embodiments, a multivariate analysis does not require data from all variables. Accordingly, in one aspect, the at least two polymorphism may comprise two polymorphisms, or alternatively three polymorphisms, or alternatively four polymorphisms, or alternatively five polymorphisms.

[0143] In one aspect, the at least two polymorphisms comprise VEGF G-634C. In another aspect, the at least two polymorphisms comprise VEGF G-634C and CXCR2 C+785T.

[0144] In one aspect of each of the above methods, the suitable mathematical algorithm of step b) is selected from the group: recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal component analysis. In one aspect, the suitable mathematical algorithm of step b) is recursive partitioning.

[0145] Also provided is a method for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF G-634C, VEGF C-1498T, CXCR2 C+785T, or WNK1 rs11064560 T>G, wherein a genotype of:

a) (A/C or A/A) for ERCC1 3'UTR C>A;
 b) (A/T or A/A) for KDR exon 11 T>A;
 c) (G/G or C/C) for VEGF G-634C;
 d) (C/C or T/T) for VEGF C-1498T
 e) (T/T or C/T) for CXCR2 C+785T; or
 f) (T/T or G/T) for WNK1 rs11064560 T>G,
 identifies the patient as likely to experience a longer progression free survival, or a genotype of:

g) (C/C) for ERCC1 3'UTR C>A;
 h) (T/T) for KDR exon 11 T>A;
 i) (G/C) for VEGF G-634C;
 j) (C/T) for VEGF C-1498T
 k) (C/C) for CXCR2 C+785T; or
 l) (G/G) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a shorter progression free survival.

Alternatively, the presence of none of a) to f) identifies the patient as likely to experience a shorter progress free survival.

[0146] In one aspect, a genotype of:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- d) (C/C or T/T) for VEGF C-1498T
- 5 e) (T/T or C/T) for CXCR2 C+785T; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a longer progression free survival.

[0147] In one aspect, a patient having a genotype of a group that is likely to experience a longer progression free survival is a patient that is likely to experience a relatively longer progression free survival than patients suffering from the cancer and receiving the therapy and having a genotype not in the group.

[0148] Also provided is a method for identifying a patient having a cancer more or less likely to respond to an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for two polymorphisms of the group COX2 G-765C or WNK1 rs11064560 T>G, wherein a genotype of:

a) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G, identifies the patient as more likely to respond to the therapy, or a genotype that is not a) identifies the patient as less likely to respond to the therapy.

[0149] In one aspect, a patient having a genotype that is more likely to respond to the therapy is a patient that is relatively more likely to respond to the therapy than patients suffering from the cancer and receiving the therapy and not having the genotype.

[0150] Also provided is a method for identifying a patient having a cancer more or less likely to respond to an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for an ICAM1 T469C polymorphism, wherein a genotype of (C/C) for ICAM1 T469C identifies the patient as more likely to respond to the therapy, or a genotype of (T/T or C/T) for ICAM1 T469C identifies the patient as less likely to respond to the therapy.

[0151] In one aspect, a genotype of (C/C) for ICAM1 T469C identifies the patient as more likely to respond to the therapy

[0152] In some embodiments, a patient having a genotype that is more likely to respond to the therapy is a patient that is relatively more likely to respond to the therapy than patients
5 suffering from the cancer and receiving the therapy and not having the genotype.

[0153] In one aspect of each of the above methods, wherein the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of administration of an anti-VEGF antibody, a VEGF inhibitor, or equivalents thereof. In one aspect, the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further
10 consists of, administration of bevacizumab or an equivalent thereof. In another aspect, the anti-VEGF-based therapy further comprises, or alternatively consists essentially of, or yet further consists of, administration of a platinum drug. In one aspect, the platinum drug is carboplatin or an equivalent thereof. In one aspect, the anti-VEGF-based therapy further comprises, or alternatively consists essentially of, or yet further consists of, administration
15 of a mitotic inhibitor. A non-limiting example of mitotic inhibitor is paclitaxel or an equivalent thereof.

[0154] In one aspect of each of the above methods, the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of administration of an anti-VEGF antibody in combination with a platinum drug and a mitotic inhibitor. In
20 one aspect of each of the above methods, the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of, administration of bevacizumab or an equivalent thereof in combination with carboplatin or an equivalent thereof, and paclitaxel or an equivalent thereof. For these therapies, the administration of the anti-VEGF antibody, the platinum drug or the mitotic inhibitor is concurrent or
25 sequential.

[0155] Also provided is a method for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the
30 patient for at least two polymorphisms of the group VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A, wherein a genotype of:

a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;
b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G) for VEGF G-1154A; or

c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or A/A) for VEGF G-1154A,

identifies the patient as likely to experience a longer overall survival, or a genotype not in the group a), b) or c) identifies the patient as likely to experience a shorter overall survival.

[0156] In one aspect, the at least two polymorphisms comprise VEGF G-634C and IL-8 T-251A and wherein the genotype of a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A identifies the patient as likely to experience a longer overall survival. As used in these methods, a patient having a genotype of a group that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than patients suffering from the cancer and receiving the therapy and not having a genotype of the group.

[0157] Also provided is a method for predicting overall survival of a cancer patient receiving a platinum drug and mitotic inhibitor combination therapy, comprising:

a) determining genotypes for at least two polymorphisms of the group VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A in a cell or tissue sample isolated from the patient; and

b) combining the genotypes using a suitable mathematical algorithm to predict the length of overall survival of the patient.

[0158] In one aspect, at least two polymorphisms comprise at least three polymorphisms of the group. In another aspect, the at least two polymorphisms comprise at least four polymorphisms of the group. In some embodiments, a multivariate analysis does not require data from all variables. Accordingly, in one aspect, the at least two polymorphism may comprise two polymorphisms, or alternatively three polymorphisms, or alternatively four polymorphisms, or alternatively five polymorphisms.

[0159] In one aspect, the at least two polymorphisms comprise VEGF G-634C. In another aspect, the at least two polymorphisms comprise VEGF G-634C and IL-8 T-251A.

[0160] For these prediction methods, the suitable mathematical algorithm of step b) is selected from the group: recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal component analysis. In one aspect, the suitable mathematical algorithm of step b) is recursive partitioning.

- 5 **[0161]** Also provided is a method for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T,
 10 ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF C-1498T, VEGF G-1154A, EGF A+61G, or COX2 G-765C, wherein a genotype of:

- a) (T/T or C/C) for ICAM1 T469C;
 b) (C/T or T/T) for CXCR2 C+785T;
 c) (A/C or A/A) for ERCC1 3'UTR C>A;
 15 d) (A/T or A/A) for KDR exon 11 T>A;
 e) (T/T or C/T) for VEGF C-1498T;
 f) (G/G or A/G) for VEGF G-1154A; or
 g) (C/C or C/G) for COX2 G-765C,

identifies the patient as likely to experience a longer overall survival, or a genotype of:

- 20 h) (C/T) for ICAM1 T469C;
 i) (C/C) for CXCR2 C+785T;
 j) (C/C) for ERCC1 3'UTR C>A;
 k) (T/T) for KDR exon 11 T>A;
 l) (C/C) for VEGF C-1498T;
 25 m) (A/A) for VEGF G-1154A; or
 n) (G/G) for COX2 G-765C,

identifies the patient as likely to experience a shorter overall survival. Alternatively, the presence of none of a) to g) identifies the patient as likely to experience a shorter overall survival.

- 30 **[0162]** In one aspect, a genotype of:

- a) (T/T or C/C) for ICAM1 T469C;

- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (T/T or C/T) for VEGF C-1498T;
- 5 f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

identifies the patient as likely to experience a longer overall survival.

[0163] In one aspect, a patient having a genotype of a group that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than patients suffering from the cancer and receiving the therapy and having a genotype not in the group.

[0164] Also provided is a method for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A, wherein a genotype of:

- a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11 T>A;
- 20 b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
- c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,

identifies the patient as likely to experience a longer progression free survival, or a genotype not in the group a) or b) identifies the patient as likely to experience a shorter progression free survival.

[0165] In one aspect, the at least two polymorphisms comprise ERCC1 3'UTR C>A and KDR exon 11 T>A and wherein the genotype of a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11 T>A identifies the patient as likely to experience a longer progression free survival.

[0166] In one aspect, a patient having a genotype of a group that is likely to experience a longer progression free survival is a patient that is likely to experience a relatively longer

progression free survival than patients suffering from the cancer and receiving the therapy and not having a genotype of the group.

Also provided is a method for predicting progression free survival of a cancer patient receiving a platinum drug and mitotic inhibitor combination therapy, comprising:

- 5 a) determining genotypes for at least two polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A in a cell or tissue sample isolated from the patient; and
- b) combining the genotypes using a suitable mathematical algorithm to predict the length of progression free survival of the patient.

10 **[0167]** In one aspect, the at least two polymorphisms comprise at least three polymorphisms of the group. In one aspect, the at least two polymorphisms comprise ERCC1 3'UTR C>A. In another aspect, the at least two polymorphisms comprise ERCC1 3'UTR C>A and KDR exon 11 T>A. In some embodiments, a multivariate analysis does not require data from all variables. Accordingly, in one aspect, the at least two
15 polymorphism may comprise two polymorphisms, or alternatively three polymorphisms.

[0168] For each of the prediction methods, the suitable mathematical algorithm of step b) is selected from the group: recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal component analysis. In one aspect, the suitable mathematical algorithm of step b) is recursive
20 partitioning.

[0169] Also provided is a method for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from
25 the patient for at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, EGF A+61G, and GSTP1 A105G, wherein a genotype of:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or A/G) for EGF A+61G; or

d) (A/A or G/G) for GSTP1 A105G,
identifies the patient as likely to experience a longer progression free survival, or a genotype of:

- e) (C/C) for ERCC1 3'UTR C>A;
- 5 f) (T/T) for KDR exon 11 T>A;
- g) (A/A) for EGF A+61G; or
- h) (A/G) for GSTP1 A105G,

identifies the patient as likely to experience a shorter progression free survival.

Alternatively, the presence of none of a) to d) identifies the patient as likely to experience a
10 shorter progression free survival.

[0170] In one aspect, a genotype of:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or A/G) for EGF A+61G; or
- 15 d) (A/A or G/G) for GSTP1 A105G,

identifies the patient as likely to experience a longer progression free survival.

[0171] In some embodiments, a patient having a genotype of a group that is likely to experience a longer progression free survival is a patient that is likely to experience a relatively longer progression free survival than patients suffering from the cancer and
20 receiving the therapy and having a genotype not in the group.

[0172] For the cancer patients receiving a platinum drug and mitotic inhibitor combination therapy, the platinum drug and mitotic inhibitor combination therapy comprises, or alternatively consists essentially of, or yet further consists of, administration of a platinum drug and a mitotic inhibitor. In one aspect, the platinum drug is carboplatin or an equivalent
25 thereof. In one aspect, the mitotic inhibitor is paclitaxel or an equivalent thereof. In some embodiments, the administration of the platinum drug and mitotic inhibitor is concurrent or sequential.

[0173] Also provided is a method of identifying a patient having a cancer more or less likely to experience a side effect from a chemotherapy, comprising, or alternatively
30 consisting essentially of, or yet further consisting of, determining a genotype of a cell or

tissue sample isolated from the patient for a WNK1 rs110644560 G>T polymorphism, wherein a genotype of (T/T) for WNK1 rs110644560 G>T identifies the patient as more likely to experience the side effect, or a genotype of (G/G or G/T) for WNK1 rs110644560 G>T identifies the patient as less likely to experience the side effect.

5 **[0174]** In one aspect, a genotype of (T/T) for WNK1 rs110644560 G>T identifies the patient as more likely to experience the side effect. In another aspect, a genotype of (G/G or G/T) for WNK1 rs110644560 G>T identifies the patient as less likely to experience the side effect.

10 **[0175]** In one aspect, a patient more likely to experience the side effect is a patient that is more likely to experience the side effect than patients having the cancer and receiving the therapy and having a genotype of (G/G or G/T) for WNK1 rs110644560 G>T. In another aspect, a patient less likely to experience the side effect is a patient that is relatively less likely to experience the side effect than patients having the cancer and receiving the therapy and having a genotype of (T/T) for WNK1 rs110644560 G>T. In one aspect, the side effect
15 is hypertension.

[0176] In some embodiments, the chemotherapy is an anti-VEGF-based therapy or a platinum drug and mitotic inhibitor combination therapy. In one aspect, the chemotherapy comprises, or alternatively consists essentially of, or yet further consists of, administration of carboplatin or an equivalent thereof in combination with paclitaxel or an equivalent
20 thereof. In another aspect, the chemotherapy comprises, or alternatively consists essentially of, or yet further consists of, administration of bevacizumab or an equivalent thereof in combination with carboplatin or an equivalent thereof and paclitaxel or an equivalent thereof.

[0177] In one aspect of each of the above methods, the cancer patient is suffering from at
25 least one cancer of the type of the group: metastatic or non-metastatic rectal cancer, metastatic or non-metastatic colon cancer, metastatic or non-metastatic colorectal cancer, non-small cell lung cancer (NSCLC), metastatic breast cancer, non-metastatic breast cancer, renal cell carcinoma, glioblastoma multiforme, ovarian cancer, hormone-refractory prostate cancer, non-metastatic unresectable liver cancer, head and neck cancer, advanced Kaposi's
30 sarcoma, or metastatic or unresectable locally advanced pancreatic cancer. In another

aspect, the cancer patient is suffering from lung cancer. In another aspect, the lung cancer is non-small cell lung cancer.

[0178] In some embodiments, the predicted overall survival or progress free survival may be a range of weeks or months of survival. In some embodiments, the predicted response
5 may be a likely complete response or partial response.

[0179] In one aspect of each of the above methods, the sample comprises, or alternatively consists essentially of, or yet further consists of at least one of a tumor cell, a normal cell adjacent to a tumor, a normal cell corresponding to the tumor tissue type, a blood cell, a peripheral blood lymphocyte, or combinations thereof. Also In one aspect of each of the
10 above methods, the sample is at least one of a fixed tissue, a frozen tissue, a biopsy tissue, a resection tissue, a microdissected tissue, or combinations thereof. A “normal cell corresponding to the tumor tissue type” refers to a normal cell from a same tissue type as the tumor tissue, such as a lung cell from a patient having lung tumor.

[0180] Suitable patient samples in the methods include, but are not limited to a sample
15 comprises, or alternatively consisting essentially of, or yet further consisting of, at least one of a tumor cell, a normal cell adjacent to a tumor, a normal cell corresponding to the tumor tissue type, a blood cell, a peripheral blood lymphocyte, or combinations thereof. The samples can be at least one of a fixed tissue, a frozen tissue, a biopsy tissue, a resection tissue, a microdissected tissue, or combinations thereof.

20 [0181] Methods to determine the genotype of the patient sample can comprise, or alternatively consisting essentially of, or yet further consist of PCR, PCR-RFLP, sequencing, or microarray.

[0182] The methods are useful in the assistance of an animal, a mammal or yet further a human patient. For the purpose of illustration only, a mammal includes but is not limited to
25 a simian, a murine, a bovine, an equine, a porcine or an ovine.

[0183] In one aspect of each of the above methods, the genotype is determined by a method comprising, or alternatively consisting essentially of, or yet further consisting of, PCR, PCR-RFLP, sequencing, or microarray.

Diagnostic Methods

[0184] As noted above, the invention further provides diagnostic, prognostic and therapeutic methods, which are based, at least in part, on determination of the identity of the polymorphic region or the gene expression level of the genes identified herein.

5 Polymorphic Region

[0185] For example, information obtained using the diagnostic assays described herein is useful for determining if a subject will likely, more likely, or less likely to respond to cancer treatment of a given type. Based on the prognostic information, a doctor can recommend a therapeutic protocol, useful for treating reducing the malignant mass or tumor in the patient
10 or treat cancer in the individual.

[0186] In addition, knowledge of the identity of a particular allele in an individual (the gene profile) allows customization of therapy for a particular disease to the individual's genetic profile, the goal of "pharmacogenomics". For example, an individual's genetic profile can enable a doctor: 1) to more effectively prescribe a drug that will address the
15 molecular basis of the disease or condition; 2) to better determine the appropriate dosage of a particular drug and 3) to identify novel targets for drug development. The identity of the genotype or expression patterns of individual patients can then be compared to the genotype or expression profile of the disease to determine the appropriate drug and dose to administer to the patient.

[0187] The ability to target populations expected to show the highest clinical benefit, based on the normal or disease genetic profile, can enable: 1) the repositioning of marketed drugs with disappointing market results; 2) the rescue of drug candidates whose clinical development has been discontinued as a result of safety or efficacy limitations, which are patient subgroup-specific; and 3) an accelerated and less costly development for drug
20 candidates and more optimal drug labeling.

[0188] Detection of point mutations or additional base pair repeats can be accomplished by molecular cloning of the specified allele and subsequent sequencing of that allele using techniques known in the art, in some aspects, after isolation of a suitable nucleic acid sample using methods known in the art. Alternatively, the gene sequences can be amplified
30 directly from a genomic DNA preparation from the tumor tissue using PCR, and the

sequence composition is determined from the amplified product. As described more fully below, numerous methods are available for isolating and analyzing a subject's DNA for mutations at a given genetic locus such as the gene of interest.

5 [0189] A detection method is allele specific hybridization using probes overlapping the polymorphic site and having about 5, or alternatively 10, or alternatively 20, or alternatively 25, or alternatively 30 nucleotides around the polymorphic region. In another embodiment of the invention, several probes capable of hybridizing specifically to the allelic variant are attached to a solid phase support, e.g., a "chip". Oligonucleotides can be bound to a solid support by a variety of processes, including lithography. For example a chip can hold up to
10 250,000 oligonucleotides (GeneChip, Affymetrix). Mutation detection analysis using these chips comprising oligonucleotides, also termed "DNA probe arrays" is described e.g., in Cronin et al. (1996) Human Mutation 7:244.

[0190] In other detection methods, it is necessary to first amplify at least a portion of the gene of interest prior to identifying the allelic variant. Amplification can be performed, e.g.,
15 by PCR and/or LCR, according to methods known in the art. In one embodiment, genomic DNA of a cell is exposed to two PCR primers and amplification for a number of cycles sufficient to produce the required amount of amplified DNA.

[0191] Alternative amplification methods include: self sustained sequence replication (Guatelli et al. (1990) Proc. Natl. Acad. Sci. USA 87:1874-1878), transcriptional
20 amplification system (Kwoh et al. (1989) Proc. Natl. Acad. Sci. USA 86:1173-1177), Q-Beta Replicase (Lizardi et al. (1988) Bio/Technology 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques known to those of skill in the art. These detection schemes are useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

25 [0192] In one embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence at least a portion of the gene of interest and detect allelic variants, e.g., mutations, by comparing the sequence of the sample sequence with the corresponding wild-type (control) sequence. Exemplary sequencing reactions include those based on techniques developed by Maxam and Gilbert (1997) Proc. Natl. Acad. Sci, USA
30 74:560) or Sanger et al. (1977) Proc. Nat. Acad. Sci, 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the

subject assays (Biotechniques (1995) **19**:448), including sequencing by mass spectrometry (see, for example, U.S. Patent No. 5,547,835 and International Patent Application Publication Number WO 94/16101, entitled DNA Sequencing by Mass Spectrometry by Koster; U.S. Patent No. 5,547,835 and international patent application Publication Number
5 WO 94/21822 entitled “DNA Sequencing by Mass Spectrometry Via Exonuclease Degradation” by Koster; U.S. Patent No. 5,605,798 and International Patent Application No. PCT/US96/03651 entitled DNA Diagnostics Based on Mass Spectrometry by Koster; Cohen et al. (1996) Adv. Chromat. **36**:127-162; and Griffin et al. (1993) Appl. Biochem. Bio. **38**:147-159). It will be evident to one skilled in the art that, for certain embodiments,
10 the occurrence of only one, two or three of the nucleic acid bases need be determined in the sequencing reaction. For instance, A-track or the like, e.g., where only one nucleotide is detected, can be carried out.

[0193] Yet other sequencing methods are disclosed, e.g., in U.S. Patent No. 5,580,732 entitled “Method of DNA Sequencing Employing A Mixed DNA-Polymer Chain Probe”
15 and U.S. Patent No. 5,571,676 entitled “Method For Mismatch-Directed *In Vitro* DNA Sequencing.”

[0194] In some cases, the presence of the specific allele in DNA from a subject can be shown by restriction enzyme analysis. For example, the specific nucleotide polymorphism can result in a nucleotide sequence comprising a restriction site which is absent from the
20 nucleotide sequence of another allelic variant.

[0195] In a further embodiment, protection from cleavage agents (such as a nuclease, hydroxylamine or osmium tetroxide and with piperidine) can be used to detect mismatched bases in RNA/RNA DNA/DNA, or RNA/DNA heteroduplexes (see, e.g., Myers et al. (1985) Science **230**:1242). In general, the technique of “mismatch cleavage” starts by
25 providing heteroduplexes formed by hybridizing a control nucleic acid, which is optionally labeled, e.g., RNA or DNA, comprising a nucleotide sequence of the allelic variant of the gene of interest with a sample nucleic acid, e.g., RNA or DNA, obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as duplexes formed based on basepair mismatches
30 between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digest the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can

be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine whether the control and sample nucleic acids have an identical nucleotide sequence or in which nucleotides they are different. See, for example, U.S. Patent No. 6,455,249, Cotton et al. (1988) Proc. Natl. Acad. Sci. USA **85**:4397; Saleeba et al. (1992) Methods Enzy. **217**:286-295. In another embodiment, the control or sample nucleic acid is labeled for detection.

[0196] In other embodiments, alterations in electrophoretic mobility is used to identify the particular allelic variant. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita et al. (1989) Proc. Natl. Acad. Sci USA **86**:2766; Cotton (1993) Mutat. Res. **285**:125-144 and Hayashi (1992) Genet Anal Tech. Appl. **9**:73-79). Single-stranded DNA fragments of sample and control nucleic acids are denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In another preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) Trends Genet. **7**:5).

[0197] In yet another embodiment, the identity of the allelic variant is obtained by analyzing the movement of a nucleic acid comprising the polymorphic region in polyacrylamide gels containing a gradient of denaturant, which is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al. (1985) Nature **313**:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing agent gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) Biophys. Chem. **265**:1275).

[0198] Examples of techniques for detecting differences of at least one nucleotide between 2 nucleic acids include, but are not limited to, selective oligonucleotide

hybridization, selective amplification, or selective primer extension. For example, oligonucleotide probes may be prepared in which the known polymorphic nucleotide is placed centrally (allele-specific probes) and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) Nature 5 324:163); Saiki et al. (1989) Proc. Natl. Acad. Sci. USA 86:6230 and Wallace et al. (1979) Nucl. Acids Res. 6:3543). Such allele specific oligonucleotide hybridization techniques may be used for the detection of the nucleotide changes in the polymorphic region of the gene of interest. For example, oligonucleotides having the nucleotide sequence of the specific allelic variant are attached to a hybridizing membrane and this membrane is then 10 hybridized with labeled sample nucleic acid. Analysis of the hybridization signal will then reveal the identity of the nucleotides of the sample nucleic acid.

[0199] Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the allelic variant of interest in the 15 center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al. (1989) Nucleic Acids Res. 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) Tibtech 11:238 and Newton et al. (1989) Nucl. Acids Res. 17:2503). This technique is also termed "PROBE" for Probe Oligo Base Extension. In addition it may be 20 desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al. (1992) Mol. Cell Probes 6:1).

[0200] In another embodiment, identification of the allelic variant is carried out using an oligonucleotide ligation assay (OLA), as described, e.g., in U.S. Patent No. 4,998,617 and in Landegren et al. (1988) Science 241:1077-1080. The OLA protocol uses two 25 oligonucleotides which are designed to be capable of hybridizing to abutting sequences of a single strand of a target. One of the oligonucleotides is linked to a separation marker, e.g., biotinylated, and the other is detectably labeled. If the precise complementary sequence is found in a target molecule, the oligonucleotides will hybridize such that their termini abut, and create a ligation substrate. Ligation then permits the labeled oligonucleotide to be 30 recovered using avidin, or another biotin ligand. Nickerson et al. have described a nucleic acid detection assay that combines attributes of PCR and OLA (Nickerson et al. (1990)

Proc. Natl. Acad. Sci. (U.S.A.) **87**:8923-8927). In this method, PCR is used to achieve the exponential amplification of target DNA, which is then detected using OLA.

[0201] Several techniques based on this OLA method have been developed and can be used to detect the specific allelic variant of the polymorphic region of the gene of interest.

5 For example, U.S. Patent No. 5,593,826 discloses an OLA using an oligonucleotide having 3'-amino group and a 5'-phosphorylated oligonucleotide to form a conjugate having a phosphoramidate linkage. In another variation of OLA described in Tobe et al. (1996) Nucleic Acids Res. **24**: 3728, OLA combined with PCR permits typing of two alleles in a single microtiter well. By marking each of the allele-specific primers with a unique hapten,
10 i.e. digoxigenin and fluorescein, each OLA reaction can be detected by using hapten specific antibodies that are labeled with different enzyme reporters, alkaline phosphatase or horseradish peroxidase. This system permits the detection of the two alleles using a high throughput format that leads to the production of two different colors.

[0202] In one embodiment, the single base polymorphism can be detected by using a

15 specialized exonuclease-resistant nucleotide, as disclosed, e.g., in Mundy, C. R. (U.S. Patent No. 4,656,127). According to the method, a primer complementary to the allelic sequence immediately 3' to the polymorphic site is permitted to hybridize to a target molecule obtained from a particular animal or human. If the polymorphic site on the target molecule contains a nucleotide that is complementary to the particular exonuclease-resistant
20 nucleotide derivative present, then that derivative will be incorporated onto the end of the hybridized primer. Such incorporation renders the primer resistant to exonuclease, and thereby permits its detection. Since the identity of the exonuclease-resistant derivative of the sample is known, a finding that the primer has become resistant to exonucleases reveals that the nucleotide present in the polymorphic site of the target molecule was
25 complementary to that of the nucleotide derivative used in the reaction. This method has the advantage that it does not require the determination of large amounts of extraneous sequence data.

[0203] In another embodiment of the invention, a solution-based method is used for

determining the identity of the nucleotide of the polymorphic site. Cohen, D. et al. (French
30 Patent 2,650,840; PCT Appln. No. WO91/02087). As in the Mundy method of U.S. Patent No. 4,656,127, a primer is employed that is complementary to allelic sequences immediately 3' to a polymorphic site. The method determines the identity of the nucleotide

of that site using labeled dideoxynucleotide derivatives, which, if complementary to the nucleotide of the polymorphic site will become incorporated onto the terminus of the primer.

[0204] An alternative method, known as Genetic Bit Analysis or GBA[™] is described by Goelet, P. et al. (PCT Appln. No. 92/15712). This method uses mixtures of labeled terminators and a primer that is complementary to the sequence 3' to a polymorphic site. The labeled terminator that is incorporated is thus determined by, and complementary to, the nucleotide present in the polymorphic site of the target molecule being evaluated. In contrast to the method of Cohen et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087) the method of Goelet, P. et al. supra, is preferably a heterogeneous phase assay, in which the primer or the target molecule is immobilized to a solid phase.

[0205] Recently, several primer-guided nucleotide incorporation procedures for assaying polymorphic sites in DNA have been described (Komher, J. S. et al. (1989) Nucl. Acids Res. **17**:7779-7784; Sokolov, B. P. (1990) Nucl. Acids Res. **18**:3671; Syvanen, A.-C. et al. (1990) Genomics **8**:684-692; Kuppuswamy, M. N. et al. (1991) Proc. Natl. Acad. Sci. (U.S.A.) **88**:1143-1147; Prezant, T. R. et al. (1992) Hum. Mutat. **1**:159-164; Ugozzoli, L. et al. (1992) GATA **9**:107-112; Nyren, P. et al. (1993) Anal. Biochem. **208**:171-175). These methods differ from GBA[™] in that they all rely on the incorporation of labeled deoxynucleotides to discriminate between bases at a polymorphic site. In such a format, since the signal is proportional to the number of deoxynucleotides incorporated, polymorphisms that occur in runs of the same nucleotide can result in signals that are proportional to the length of the run (Syvanen, A.-C. et al. (1993) Amer. J. Hum. Genet. **52**:46-59).

[0206] If the polymorphic region is located in the coding region of the gene of interest, yet other methods than those described above can be used for determining the identity of the allelic variant. For example, identification of the allelic variant, which encodes a mutated signal peptide, can be performed by using an antibody specifically recognizing the mutant protein in, e.g., immunohistochemistry or immunoprecipitation. Antibodies to the wild-type or signal peptide mutated forms of the signal peptide proteins can be prepared according to methods known in the art.

[0207] Often a solid phase support is used as a support capable of binding of a primer, probe, polynucleotide, an antigen or an antibody. Well-known supports include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the support can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. or alternatively polystyrene beads. Those skilled in the art will know many other suitable supports for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0208] Moreover, it will be understood that any of the above methods for detecting alterations in a gene or gene product or polymorphic variants can be used to monitor the course of treatment or therapy.

[0209] The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits, such as those described below, comprising at least one probe or primer nucleic acid described herein, which may be conveniently used, e.g., to determine whether a subject is likely responsive to the therapy as described herein or has or is at risk of developing disease such as colorectal cancer.

[0210] Sample nucleic acid for use in the above-described diagnostic and prognostic methods can be obtained from any suitable cell type or tissue of a subject. For example, a subject's bodily fluid (e.g. blood) can be obtained by known techniques (e.g., venipuncture). Alternatively, nucleic acid tests can be performed on dry samples (e.g., hair or skin). Fetal nucleic acid samples can be obtained from maternal blood as described in International Patent Application No. WO91/07660 to Bianchi. Alternatively, amniocytes or chorionic villi can be obtained for performing prenatal testing.

[0211] Diagnostic procedures can also be performed in situ directly upon tissue sections (fixed and/or frozen) of patient tissue obtained from biopsies or resections, such that no nucleic acid purification is necessary. Nucleic acid reagents can be used as probes and/or

primers for such in situ procedures (see, for example, Nuovo, G. J. (1992) PCR IN SITU HYBRIDIZATION: PROTOCOLS AND APPLICATIONS, Raven Press, NY).

[0212] In addition to methods which focus primarily on the detection of one nucleic acid sequence, profiles can also be assessed in such detection schemes. Fingerprint profiles can be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR.

[0213] Antibodies directed against wild type or mutant peptides encoded by the allelic variants of the gene of interest may also be used in disease diagnostics and prognostics. Such diagnostic methods, may be used to detect abnormalities in the level of expression of the peptide, or abnormalities in the structure and/or tissue, cellular, or subcellular location of the peptide. Protein from the tissue or cell type to be analyzed may easily be detected or isolated using techniques which are well known to one of skill in the art, including but not limited to Western blot analysis. For a detailed explanation of methods for carrying out Western blot analysis, see Sambrook and Russell (2001) supra. The protein detection and isolation methods employed herein can also be such as those described in Harlow and Lane, (1999) supra. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody (see below) coupled with light microscopic, flow cytometric, or fluorimetric detection. The antibodies (or fragments thereof) useful in the present invention may, additionally, be employed histologically, as in immunofluorescence or immunoelectron microscopy, for in situ detection of the peptides or their allelic variants. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody of the present invention. The antibody (or fragment) is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the subject polypeptide, but also its distribution in the examined tissue. Using the present invention, one of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[0214] Generally, any suitable oligonucleotide pairs that flank or hybridize to a gene of interest may be used to carry out the method of the invention. The invention provides specific oligonucleotide primers and probes that are particularly accurate in assessing the polymorphic region or expression levels of the genes of interest. However, other primers

and/or probes are described in the art and are suitable for determining the polymorphic region or expression level of the genes of interest.

[0215] In one embodiment, it is necessary to first amplify at least a portion of the gene of interest prior to identifying the polymorphic region or level of gene expression of the gene of interest in a sample. Amplification can be performed, e.g., by PCR and/or LCR,
5 according to methods known in the art. Various non-limiting examples of PCR include the herein described methods.

[0216] Allele-specific PCR is a diagnostic or cloning technique is used to identify or utilize single-nucleotide polymorphisms (SNPs). It requires prior knowledge of a DNA
10 sequence, including differences between alleles, and uses primers whose 3' ends encompass the SNP. PCR amplification under stringent conditions is much less efficient in the presence of a mismatch between template and primer, so successful amplification with an SNP-specific primer signals presence of the specific SNP in a sequence (See, Saiki et al. (1986) Nature **324**(6093):163-166 and U.S. Patent Nos.: 5,821,062; 7,052,845 or
15 7,250,258).

[0217] Assembly PCR or Polymerase Cycling Assembly (PCA) is the artificial synthesis of long DNA sequences by performing PCR on a pool of long oligonucleotides with short overlapping segments. The oligonucleotides alternate between sense and antisense
20 directions, and the overlapping segments determine the order of the PCR fragments thereby selectively producing the final long DNA product (See, Stemmer et al. (1995) Gene **164**(1):49-53 and U.S. Patent Nos.: 6,335,160; 7,058,504 or 7,323,336)

[0218] Asymmetric PCR is used to preferentially amplify one strand of the original DNA more than the other. It finds use in some types of sequencing and hybridization probing where having only one of the two complementary strands is required. PCR is carried out as
25 usual, but with a great excess of the primers for the chosen strand. Due to the slow amplification later in the reaction after the limiting primer has been used up, extra cycles of PCR are required (See, Innis et al. (1988) Proc Natl Acad Sci U.S.A. **85**(24):9436-9440 and U.S. Patent Nos.: 5,576,180; 6,106,777 or 7,179,600) A recent modification on this process, known as **Linear-After-The-Exponential-PCR (LATE-PCR)**, uses a limiting primer with a
30 higher melting temperature (T_m) than the excess primer to maintain reaction efficiency as

the limiting primer concentration decreases mid-reaction (Pierce et al. (2007) *Methods Mol. Med.* **132**:65-85).

[0219] Colony PCR uses bacterial colonies, for example *E. coli*, which can be rapidly screened by PCR for correct DNA vector constructs. Selected bacterial colonies are picked with a sterile toothpick and dabbed into the PCR master mix or sterile water. The PCR is started with an extended time at 95°C when standard polymerase is used or with a shortened denaturation step at 100°C and special chimeric DNA polymerase (Pavlov et al. (2006) "Thermostable DNA Polymerases for a Wide Spectrum of Applications: Comparison of a Robust Hybrid TopoTaq to other enzymes", in Kieleczawa J: *DNA Sequencing II: Optimizing Preparation and Cleanup*. Jones and Bartlett, pp. 241-257)

[0220] Helicase-dependent amplification is similar to traditional PCR, but uses a constant temperature rather than cycling through denaturation and annealing/extension cycles. DNA Helicase, an enzyme that unwinds DNA, is used in place of thermal denaturation (See, Myriam et al. (2004) *EMBO reports* **5**(8):795–800 and U.S. Patent No. 7,282,328).

[0221] Hot-start PCR is a technique that reduces non-specific amplification during the initial set up stages of the PCR. The technique may be performed manually by heating the reaction components to the melting temperature (e.g., 95°C) before adding the polymerase (Chou et al. (1992) *Nucleic Acids Research* **20**:1717-1723 and U.S. Patent Nos.: 5,576,197 and 6,265,169). Specialized enzyme systems have been developed that inhibit the polymerase's activity at ambient temperature, either by the binding of an antibody (Sharkey et al. (1994) *Bio/Technology* **12**:506-509) or by the presence of covalently bound inhibitors that only dissociate after a high-temperature activation step. Hot-start/cold-finish PCR is achieved with new hybrid polymerases that are inactive at ambient temperature and are instantly activated at elongation temperature.

[0222] Intersequence-specific (ISSR) PCR method for DNA fingerprinting that amplifies regions between some simple sequence repeats to produce a unique fingerprint of amplified fragment lengths (Zietkiewicz et al. (1994) *Genomics* **20**(2):176-83).

[0223] Inverse PCR is a method used to allow PCR when only one internal sequence is known. This is especially useful in identifying flanking sequences to various genomic inserts. This involves a series of DNA digestions and self ligation, resulting in known

sequences at either end of the unknown sequence (Ochman et al. (1988) Genetics **120**:621-623 and U.S. Patent Nos.: 6,013,486; 6,106,843 or 7,132,587).

[0224] Ligation-mediated PCR uses small DNA linkers ligated to the DNA of interest and multiple primers annealing to the DNA linkers; it has been used for DNA sequencing,
5 genome walking, and DNA footprinting (Mueller et al. (1988) Science **246**:780-786).

[0225] Methylation-specific PCR (MSP) is used to detect methylation of CpG islands in genomic DNA (Herman et al. (1996) Proc Natl Acad Sci U.S.A. **93**(13):9821-9826 and U.S. Patent Nos.: 6,811,982; 6,835,541 or 7,125,673). DNA is first treated with sodium bisulfite, which converts unmethylated cytosine bases to uracil, which is recognized by PCR primers
10 as thymine. Two PCRs are then carried out on the modified DNA, using primer sets identical except at any CpG islands within the primer sequences. At these points, one primer set recognizes DNA with cytosines to amplify methylated DNA, and one set recognizes DNA with uracil or thymine to amplify unmethylated DNA. MSP using qPCR can also be performed to obtain quantitative rather than qualitative information about
15 methylation.

[0226] Multiplex Ligation-dependent Probe Amplification (MLPA) permits multiple targets to be amplified with only a single primer pair, thus avoiding the resolution limitations of multiplex PCR (see below).

[0227] Multiplex-PCR uses of multiple, unique primer sets within a single PCR mixture
20 to produce amplicons of varying sizes specific to different DNA sequences (See, U.S. Patent Nos.: 5,882,856; 6,531,282 or 7,118,867). By targeting multiple genes at once, additional information may be gained from a single test run that otherwise would require several times the reagents and more time to perform. Annealing temperatures for each of the primer sets must be optimized to work correctly within a single reaction, and amplicon
25 sizes, i.e., their base pair length, should be different enough to form distinct bands when visualized by gel electrophoresis.

[0228] Nested PCR increases the specificity of DNA amplification, by reducing background due to non-specific amplification of DNA. Two sets of primers are being used in two successive PCRs. In the first reaction, one pair of primers is used to generate DNA
30 products, which besides the intended target, may still consist of non-specifically amplified

DNA fragments. The product(s) are then used in a second PCR with a set of primers whose binding sites are completely or partially different from and located 3' of each of the primers used in the first reaction (See, U.S. Patent Nos.: 5,994,006; 7,262,030 or 7,329,493).

Nested PCR is often more successful in specifically amplifying long DNA fragments than
5 conventional PCR, but it requires more detailed knowledge of the target sequences.

[0229] Overlap-extension PCR is a genetic engineering technique allowing the construction of a DNA sequence with an alteration inserted beyond the limit of the longest practical primer length.

[0230] Quantitative PCR (Q-PCR), also known as RQ-PCR, QRT-PCR and RTQ-PCR, is
10 used to measure the quantity of a PCR product following the reaction or in real-time. See, U.S. Patent Nos.: 6,258,540; 7,101,663 or 7,188,030. Q-PCR is the method of choice to quantitatively measure starting amounts of DNA, cDNA or RNA. Q-PCR is commonly used to determine whether a DNA sequence is present in a sample and the number of its copies in the sample. The method with currently the highest level of accuracy is digital
15 PCR as described in U.S. Patent No. 6,440,705; U.S. Publication No. 2007/0202525; Dressman et al. (2003) Proc. Natl. Acad. Sci USA **100**(15):8817-8822 and Vogelstein et al. (1999) Proc. Natl. Acad. Sci. USA. **96**(16):9236-9241. More commonly, RT-PCR refers to reverse transcription PCR (see below), which is often used in conjunction with Q-PCR. QRT-PCR methods use fluorescent dyes, such as Sybr Green, or fluorophore-containing
20 DNA probes, such as TaqMan, to measure the amount of amplified product in real time.

[0231] Reverse Transcription PCR (RT-PCR) is a method used to amplify, isolate or identify a known sequence from a cellular or tissue RNA (See, U.S. Patent Nos.: 6,759,195; 7,179,600 or 7,317,111). The PCR is preceded by a reaction using reverse transcriptase to convert RNA to cDNA. RT-PCR is widely used in expression profiling, to determine the
25 expression of a gene or to identify the sequence of an RNA transcript, including transcription start and termination sites and, if the genomic DNA sequence of a gene is known, to map the location of exons and introns in the gene. The 5' end of a gene (corresponding to the transcription start site) is typically identified by an RT-PCR method, named Rapid Amplification of cDNA Ends (RACE-PCR).

[0232] Thermal asymmetric interlaced PCR (TAIL-PCR) is used to isolate unknown
30 sequence flanking a known sequence. Within the known sequence TAIL-PCR uses a nested

pair of primers with differing annealing temperatures; a degenerate primer is used to amplify in the other direction from the unknown sequence (Liu et al. (1995) *Genomics* **25**(3):674-81).

[0233] Touchdown PCR a variant of PCR that aims to reduce nonspecific background by gradually lowering the annealing temperature as PCR cycling progresses. The annealing temperature at the initial cycles is usually a few degrees (3-5°C) above the T_m of the primers used, while at the later cycles, it is a few degrees (3-5°C) below the primer T_m . The higher temperatures give greater specificity for primer binding, and the lower temperatures permit more efficient amplification from the specific products formed during the initial cycles (Don et al. (1991) *Nucl Acids Res* **19**:4008 and U.S. Patent No. 6,232,063).

[0234] In one embodiment of the invention, probes are labeled with two fluorescent dye molecules to form so-called “molecular beacons” (Tyagi, S. and Kramer, F.R. (1996) *Nat. Biotechnol.* **14**:303-8). Such molecular beacons signal binding to a complementary nucleic acid sequence through relief of intramolecular fluorescence quenching between dyes bound to opposing ends on an oligonucleotide probe. The use of molecular beacons for genotyping has been described (Kostrikis, L.G. (1998) *Science* **279**:1228-9) as has the use of multiple beacons simultaneously (Marras, S.A. (1999) *Genet. Anal.* **14**:151-6). A quenching molecule is useful with a particular fluorophore if it has sufficient spectral overlap to substantially inhibit fluorescence of the fluorophore when the two are held proximal to one another, such as in a molecular beacon, or when attached to the ends of an oligonucleotide probe from about 1 to about 25 nucleotides.

[0235] Labeled probes also can be used in conjunction with amplification of a gene of interest. (Holland et al. (1991) *Proc. Natl. Acad. Sci.* **88**:7276-7280). U.S. Patent No. 5,210,015 by Gelfand et al. describe fluorescence-based approaches to provide real time measurements of amplification products during PCR. Such approaches have either employed intercalating dyes (such as ethidium bromide) to indicate the amount of double-stranded DNA present, or they have employed probes containing fluorescence-quencher pairs (also referred to as the “Taq-Man” approach) where the probe is cleaved during amplification to release a fluorescent molecule whose concentration is proportional to the amount of double-stranded DNA present. During amplification, the probe is digested by the nuclease activity of a polymerase when hybridized to the target sequence to cause the fluorescent molecule to be separated from the quencher molecule, thereby causing

fluorescence from the reporter molecule to appear. The Taq-Man approach uses a probe containing a reporter molecule--quencher molecule pair that specifically anneals to a region of a target polynucleotide containing the polymorphism.

[0236] Probes can be affixed to surfaces for use as "gene chips." Such gene chips can be used to detect genetic variations by a number of techniques known to one of skill in the art. In one technique, oligonucleotides are arrayed on a gene chip for determining the DNA sequence of a by the sequencing by hybridization approach, such as that outlined in U.S. Patent Nos. 6,025,136 and 6,018,041. The probes of the invention also can be used for fluorescent detection of a genetic sequence. Such techniques have been described, for example, in U.S. Patent Nos. 5,968,740 and 5,858,659. A probe also can be affixed to an electrode surface for the electrochemical detection of nucleic acid sequences such as described by Kayem et al. U.S. Patent No. 5,952,172 and by Kelley, S.O. et al. (1999) Nucleic Acids Res. 27:4830-4837.

[0237] This invention also provides for a prognostic panel of genetic markers selected from, but not limited to the genetic polymorphisms or gene expression levels identified herein. The prognostic panel comprises, or alternatively consists essentially of, or yet further consists of, probes or primers that can be used to amplify and/or for determining the molecular structure of the polymorphisms or the gene expression levels identified herein. The probes or primers can be attached or supported by a solid phase support such as, but not limited to a gene chip or microarray. The probes or primers can be detectably labeled. This aspect of the invention is a means to identify the genotype of a patient sample for the genes of interest identified above.

[0238] In one aspect, the panel contains the herein identified probes or primers as wells as other probes or primers. In a alternative aspect, the panel includes one or more of the above noted probes or primers and others. In a further aspect, the panel consist only of the above-noted probes or primers.

[0239] Primers or probes can be affixed to surfaces for use as "gene chips" or "microarray." Such gene chips or microarrays can be used to detect genetic variations by a number of techniques known to one of skill in the art. In one technique, oligonucleotides are arrayed on a gene chip for determining the DNA sequence of a by the sequencing by hybridization approach, such as that outlined in U.S. Patent Nos. 6,025,136 and 6,018,041.

The probes of the invention also can be used for fluorescent detection of a genetic sequence. Such techniques have been described, for example, in U.S. Patent Nos. 5,968,740 and 5,858,659. A probe also can be affixed to an electrode surface for the electrochemical detection of nucleic acid sequences such as described by Kayem et al. U.S. Patent No. 5,952,172 and by Kelley et al. (1999) *Nucleic Acids Res.* **27**:4830-4837.

[0240] Various “gene chips” or “microarray” and similar technologies are known in the art. Examples of such include, but are not limited to LabCard (ACLARA Bio Sciences Inc.); GeneChip (Affymetric, Inc); LabChip (Caliper Technologies Corp); a low-density array with electrochemical sensing (Clinical Micro Sensors); LabCD System (Gamera Bioscience Corp.); Omni Grid (Gene Machines); Q Array (Genetix Ltd.); a high-throughput, automated mass spectrometry systems with liquid-phase expression technology (Gene Trace Systems, Inc.); a thermal jet spotting system (Hewlett Packard Company); Hyseq HyChip (Hyseq, Inc.); BeadArray (Illumina, Inc.); GEM (Incyte Microarray Systems); a high-throughput microarraying system that can dispense from 12 to 64 spots onto multiple glass slides (Intelligent Bio-Instruments); Molecular Biology Workstation and NanoChip (Nanogen, Inc.); a microfluidic glass chip (Orchid biosciences, Inc.); BioChip Arrayer with four PiezoTip piezoelectric drop-on-demand tips (Packard Instruments, Inc.); FlexJet (Rosetta Inpharmatic, Inc.); MALDI-TOF mass spectrometer (Sequenome); ChipMaker 2 and ChipMaker 3 (TeleChem International, Inc.); and GenoSensor (Vysis, Inc.) as identified and described in Heller (2002) *Annu. Rev. Biomed. Eng.* **4**:129-153. Examples of “Gene chips” or a “microarray” are also described in U.S. Patent Publ. Nos.: 2007/0111322, 2007/0099198, 2007/0084997, 2007/0059769 and 2007/0059765 and US Patent 7,138,506, 7,070,740, and 6,989,267.

[0241] In one aspect, “gene chips” or “microarrays” containing probes or primers for the gene of interest are provided alone or in combination with other probes and/or primers. A suitable sample is obtained from the patient extraction of genomic DNA, RNA, or any combination thereof and amplified if necessary. The DNA or RNA sample is contacted to the gene chip or microarray panel under conditions suitable for hybridization of the gene(s) of interest to the probe(s) or primer(s) contained on the gene chip or microarray. The probes or primers may be detectably labeled thereby identifying the polymorphism in the gene(s) of interest. Alternatively, a chemical or biological reaction may be used to identify the probes or primers which hybridized with the DNA or RNA of the gene(s) of interest.

The genetic profile of the patient is then determined with the aid of the aforementioned apparatus and methods.

Nucleic Acids

[0242] In one aspect, the nucleic acid sequences of the gene of interest, or portions thereof, can be the basis for probes or primers, e.g., in methods for determining expression level of the gene of interest or the allelic variant of a polymorphic region of a gene of interest identified in the experimental section below. Thus, they can be used in the methods of the invention to determine which therapy is most likely to treat an individual's cancer.

[0243] The methods of the invention can use nucleic acids isolated from vertebrates. In one aspect, the vertebrate nucleic acids are mammalian nucleic acids. In a further aspect, the nucleic acids used in the methods of the invention are human nucleic acids.

[0244] Primers for use in the methods of the invention are nucleic acids which hybridize to a nucleic acid sequence which is adjacent to the region of interest or which covers the region of interest and is extended. A primer can be used alone in a detection method, or a primer can be used together with at least one other primer or probe in a detection method. Primers can also be used to amplify at least a portion of a nucleic acid. Probes for use in the methods of the invention are nucleic acids which hybridize to the gene of interest and which are not further extended. For example, a probe is a nucleic acid which hybridizes to the gene of interest, and which by hybridization or absence of hybridization to the DNA of a subject will be indicative of the identity of the allelic variant of the expression levels of the gene of interest. Primers and/or probes for use in the methods can be provided as isolated single stranded oligonucleotides or alternatively, as isolated double stranded oligonucleotides.

[0245] In one embodiment, primers comprise a nucleotide sequence which comprises, or alternatively consists essentially of, or yet further consists of, a region having a nucleotide sequence which hybridizes under stringent conditions to about: 6, or alternatively 8, or alternatively 10, or alternatively 12, or alternatively 25, or alternatively 30, or alternatively 40, or alternatively 50, or alternatively 75 consecutive nucleotides of the gene of interest.

[0246] Primers can be complementary to nucleotide sequences located close to each other or further apart, depending on the use of the amplified DNA. For example, primers can be

chosen such that they amplify DNA fragments of at least about 10 nucleotides or as much as several kilobases. Preferably, the primers of the invention will hybridize selectively to nucleotide sequences located about 100 to about 1000 nucleotides apart.

[0247] For amplifying at least a portion of a nucleic acid, a forward primer (i.e., 5' primer) and a reverse primer (i.e., 3' primer) will preferably be used. Forward and reverse primers hybridize to complementary strands of a double stranded nucleic acid, such that upon extension from each primer, a double stranded nucleic acid is amplified.

[0248] Yet other preferred primers of the invention are nucleic acids which are capable of selectively hybridizing to the gene of interest. Thus, such primers can be specific for the gene of interest sequence, so long as they have a nucleotide sequence which is capable of hybridizing to the gene of interest. Examples of primers and probes useful in the herein described invention are shown in Tables 1 and 2. The VEGF allele with polymorphism G-634C is identified and described in Sfar (2006) **35**(1-2):21-28. Furthermore, the VEGF G-634C polymorphism is also known in the art as VEGF G+405C as described in Buraczynska et al. (2006) Nephrol. Dial Transplant doi:10.1093/ndt/gfl641 and Shastry et al. (2006) Graefe's Archive for Clinical and Experimental Ophthalmology **245**(5):741-743. The IL-1Ra VNTR polymorphisms are identified and described in Vijgen et al. (2002) Genes and Immunity **3**:400-406.

Table A: Probe and Primer Sequences for Determining Gene Expression Levels

Polymorphism	Forward primer	SEQ ID NO.	Reverse primer	SEQ ID NO.
COX2 G-765C	ATTCTGGCCATCGCCGC TTC	1	CTCCTTGTTTCTTGGAAAGAG ACG	2
CXCR2 C+785T	CATCTTTGCTGTCTGTC TCA	3	CTGTGAAGGATGCCCAGAAT	4
EGF A+61G	TGTCATAAAGGAAAG GA	5	TTCACAGAGTTTAACAGCCC	6
EGFR G497A	GTTTGGGACCTCCGGTC AG	7	CTTGTCACGCATTCCCTGC	8
ERCC1 3'UTR C/A	TGAGCCAATTCAGCCA CT	9	TAGTTCCTCAGTTTCCCG	10
ERCC1 C118T	GCAGAGCTCACCTGAG GAAC	11	GAGGTGCAAGAAGAGGTGGA	12
FGFR4 G388A	GACCGCAGCAGCGCCC GAGGCCAG	13	AGAGGGAAGAGGGAGAGCTT CTG	14
GSTP1 A105G	ACCCCAGGGCTCTATG GGAA	15	TGAGGGCACAAGAAGCCCT	16
ICAM1 T469C	CCATCGGGGAATCAGT G	17	ACAGAGCACATTACGGT	18
IL8 T-251A	TTGTTCTAACACCTGCC ACTCT	19	GGCAAACCTGAGTCATCACA	20
KDR EXON 11 T/A	TTTCTCCCTGGAAGTC CTC	21	GGCTGCGTTGGAAGTTATTT	22
VEGF C+936T	ACACCATCACCATCGA CAGA	23	TCGGTGATTAGCAGCAAGA	24

VEGF C-1498T	CAGCAGTTGTTACGGG CATA	25	GCCCCGAGAAGGACTTTGTACT	26
VEGF G-1154A	TTTTCAGGCTGTGAACC TTG	27	GGGACAGGCGAGCCTCAG	28
VEGF G-634C	ACTTCCCCAAATCACTG TGG	29	GTCACCTACTTTGCCCTGT	30
WNK1rs11064560 T/G	GGTACTGATAGTAGGC TGTGGTTATTG	31	CCTTTATCATCCTTAAAGGCC ATC	32
WNK1rs2158501 G/A	GGTACTGATAGTAGGC TGTGGTTATTG	33	CCTTTATCATCCTTAAAGGCC ATC	34
XPD A751C	CCTCTCCCTTTCTCTG TTC	35	CAGGTGAGGGGGACATCT	36
XPD C156A	GCCTCACAGCCTCTAT GTG	37	GCATCAAATTCCTGGGACAA	38
XRCC1 G-399A	TTGTGCTTTCTCTGTGT CCA	39	TCCTCCAGCCTTTTCTGATA	40

[0249] The probe or primer may further comprises a label attached thereto, which, e.g., is capable of being detected, e.g. the label group is selected from amongst radioisotopes, fluorescent compounds, enzymes, and enzyme co-factors.

[0250] Additionally, the isolated nucleic acids used as probes or primers may be modified to become more stable. Exemplary nucleic acid molecules which are modified include phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patent Nos. 5,176,996; 5,264,564 and 5,256,775).

[0251] The nucleic acids used in the methods of the invention can also be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule. The nucleic acids, e.g., probes or primers, may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane. See, e.g., Letsinger et al. (1989) Proc. Natl. Acad. Sci. U.S.A. **86**:6553-6556; Lemaitre et al. (1987) Proc. Natl. Acad. Sci. **84**:648-652; and PCT Publ. No. WO 88/09810, published Dec. 15, 1988), hybridization-triggered cleavage agents, (see, e.g., Krol et al. (1988) BioTechniques **6**:958-976) or intercalating agents (see, e.g., Zon (1988) Pharm. Res. **5**:539-549. To this end, the nucleic acid used in the methods of the invention may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

[0252] The isolated nucleic acids used in the methods of the invention can also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose or, alternatively, comprise at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

[0253] The nucleic acids, or fragments thereof, to be used in the methods of the invention can be prepared according to methods known in the art and described, e.g., in Sambrook et al. (2001) supra. For example, discrete fragments of the DNA can be prepared and cloned using restriction enzymes. Alternatively, discrete fragments can be prepared using the
5 Polymerase Chain Reaction (PCR) using primers having an appropriate sequence under the manufacturer's conditions, (described above).

[0254] Oligonucleotides can be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides can be
10 synthesized by the method of Stein et al. (1988) Nucl. Acids Res. **16**:3209, methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports. Sarin et al. (1988) Proc. Natl. Acad. Sci. U.S.A. **85**:7448-7451.

Methods of Treatment

[0255] The invention further provides methods of treating a cancer patient after the patient
15 is identified to likely to experience a better clinical outcome, such as longer overall survival, longer progression free survival, better response, longer time to tumor recurrence, or reduced side effects.

[0256] Thus, a method for treating a cancer patient is provided wherein the patient is selected as likely to experience a longer overall survival from receiving an anti-VEGF based
20 therapy, based on the presence of at least one genotype of the group:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- 25 e) (A/G or G/G) for GSTP1 A105G; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

in a sample isolated from the patient, comprising or alternatively consisting essentially of, or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

[0257] Use of an anti-VEGF based therapy is also provided, wherein the use is for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- 5 a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (A/G or G/G) for GSTP1 A105G; or
- 10 f) (T/T or G/T) for WNK1 rs11064560 T>G,

in a sample isolated from the patient.

[0258] Further provided is an anti-VEGF based therapy for use in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- 15 a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (A/G or G/G) for GSTP1 A105G; or
- 20 f) (T/T or G/T) for WNK1 rs11064560 T>G,

in a sample isolated from the patient, thereby treating the patient.

[0259] For these patients, the patient can be selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, GSTP1
25 A105G, or WNK1 rs11064560 T>G.

[0260] Also provided is a method for treating a cancer patient selected as likely to experience a longer overall survival from receiving an anti-VEGF based therapy, based on the presence of at least one genotype of the group:

- a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
- 30 b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or
- c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A or A/T) for IL-8 T-251A,

in a sample isolated from the patient, comprising, or alternatively consisting essentially of, or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

[0261] Further provided is the use of an anti-VEGF based therapy for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
- b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or
- c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A or A/T) for IL-8 T-251A, in a sample isolated from the patient.

[0262] Yet further provided is an anti-VEGF based therapy for use in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
- b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or
- c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A or A/T) for IL-8 T-251A, in a sample isolated from the patient.

[0263] For the above methods, patient can also be selected by determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A.

[0264] Yet further provided is a method for treating a cancer patient selected as likely to experience a longer progression free survival from receiving an anti-VEGF based therapy, based on the presence of at least one genotype of the group:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- d) (C/C or T/T) for VEGF C-1498T;
- e) (T/T or C/T) for CXCR2 C+785T; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

in a sample isolated from the patient, comprising, or alternatively consisting essentially of,

or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

[0265] This invention also provides the use of an anti-VEGF based therapy for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- 10 d) (C/C or T/T) for VEGF C-1498T;
- e) (T/T or C/T) for CXCR2 C+785T; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

in a sample isolated from the patient.

[0266] Yet further provided is an anti-VEGF based therapy for use in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- 20 d) (C/C or T/T) for VEGF C-1498T;
- e) (T/T or C/T) for CXCR2 C+785T; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

in a sample isolated from the patient.

[0267] In one aspect of each of the above noted methods, the patient can also be selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF G-634C, VEGF C-1498T, CXCR2 C+785T, or WNK1 rs11064560 T>G.

[0268] This invention also provides a method for treating a cancer patient selected as likely to experience a longer progression free survival from receiving an anti-VEGF based therapy, based on the presence of at least one genotype of the group:

- a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or

A/A) for ERCC1 3'UTR C>A; or

b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C,

in a sample isolated from the patient, comprising, or alternatively consisting essentially of,
 5 or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

[0269] Further provided is the use of an anti-VEGF based therapy for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one
 10 genotype of the group:

a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or A/A) for ERCC1 3'UTR C>A; or

b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C, in a sample isolated from the patient.

[0270] An anti-VEGF based therapy for use in treating a cancer patient is further provided. The therapy is for a patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or
 20 A/A) for ERCC1 3'UTR C>A; or

b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C, in a sample isolated from the patient.

[0271] For the above noted methods, the patient can be selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism
 25 of the group VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C.

[0272] Also provided is a method for treating a cancer patient selected as more likely to respond to an anti-VEGF based therapy, based on the presence of at least one genotype of:

a) (C/C) for ICAM1 T469C; or

30 b) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G,

in a sample isolated from the patient, comprising, or alternatively consisting essentially of,

or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

[0273] This invention also provides the use of an anti-VEGF based therapy for the manufacture of a medicament in treating a cancer patient selected as more likely to respond to an anti-VEGF based therapy, based on the presence of at least one genotype of:

- a) (C/C) for ICAM1 T469C; or
 - b) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G,
- in a sample isolated from the patient.

[0274] This invention yet further provides an anti-VEGF based therapy for use in treating a cancer patient selected as more likely to respond to an anti-VEGF based therapy, based on the presence of at least one genotype of:

- a) (C/C) for ICAM1 T469C; or
- b) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G, in a sample isolated from the patient.

[0275] For the above noted methods, the patient can also be selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, COX2 G-765C or WNK1 rs11064560 T>G.

[0276] Also provided is a method for treating a cancer patient selected as likely to experience a longer overall survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, based on the presence of at least one genotype of the group:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (T/T or C/T) for VEGF C-1498T;
- f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

in a sample isolated from the patient, comprising, or alternatively consisting essentially of, or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

[0277] Further provided is the use of a therapy comprising, or alternatively consisting essentially of, or yet further consisting of a platinum drug and a mitotic inhibitor for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one

5 genotype of the group:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- 10 e) (T/T or C/T) for VEGF C-1498T;
- f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

in a sample isolated from the patient.

[0278] Further provided is a therapy comprising a platinum drug and a mitotic inhibitor
15 for use in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- 20 d) (A/T or A/A) for KDR exon 11 T>A;
- e) (T/T or C/T) for VEGF C-1498T;
- f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

in a sample isolated from the patient.

25 **[0279]** For the above noted methods, the patient can be selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF C-1498T, VEGF G-1154A, EGF A+61G, or COX2 G-765C.

[0280] Yet further provided is a method for treating a cancer patient selected as likely to
30 experience a longer overall survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, based on the presence of at least one genotype of the group:

- a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;

b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G) for VEGF G-1154A; or

c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or A/A) for VEGF G-1154A, in a sample isolated from the patient, comprising, or alternatively
5 consisting essentially of, or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

[0281] Also provides is the use of a therapy comprising, or alternatively consisting essentially of, or yet further consisting of a platinum drug and a mitotic inhibitor for the manufacture of a medicament in treating a cancer patient selected as likely to experience a
10 longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;

b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G) for VEGF G-1154A; or

15 c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or A/A) for VEGF G-1154A, in a sample isolated from the patient.

[0282] Yet further provided is a therapy comprising, or alternatively consisting essentially of, or yet further consisting of, a platinum drug and a mitotic inhibitor for use in treating a cancer patient selected as likely to experience a longer overall survival from receiving the
20 therapy, based on the presence of at least one genotype of the group:

a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;

b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G) for VEGF G-1154A; or

25 c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or A/A) for VEGF G-1154A,
in a sample isolated from the patient.

[0283] For the above methods, the patient can be selected by determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A.

30 [0284] Also provided is a method for treating a cancer patient selected as likely to experience a longer progression free survival from receiving a therapy comprising a

platinum drug and a mitotic inhibitor, based on the presence of at least one genotype of the group:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- 5 c) (G/G or A/G) for EGF A+61G; or
- d) (A/A or G/G) for GSTP1 A105G,

in a sample isolated from the patient, comprising, or alternatively consisting essentially of, or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

- 10 **[0285]** Further provided is the use of a therapy comprising, or alternatively consisting essentially of, or yet further consisting of, a platinum drug and a mitotic inhibitor for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- 15 a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or A/G) for EGF A+61G; or
- d) (A/A or G/G) for GSTP1 A105G,

in a sample isolated from the patient.

- 20 **[0286]** Yet further provided is a therapy comprising, or alternatively consisting essentially of, or yet further consisting of, a platinum drug and a mitotic inhibitor for use in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- 25 b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or A/G) for EGF A+61G; or
- d) (A/A or G/G) for GSTP1 A105G,

in a sample isolated from the patient.

- 30 **[0287]** For the above methods the patient can also be selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, EGF A+61G, and GSTP1 A105G.

[0288] This invention provides a method for treating a cancer patient selected as likely to experience a longer progression free survival from receiving a therapy comprising, or alternatively consisting essentially of, or yet further consisting of, a platinum drug and a mitotic inhibitor, based on the presence of at least one genotype of the group:

- 5 a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11 T>A;
- b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
- c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,
- 10 in a sample isolated from the patient, comprising, or alternatively consisting essentially of, or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

[0289] Also provided is the use of a therapy comprising, or alternatively consisting essentially of, or yet further consisting of, a platinum drug and a mitotic inhibitor for the manufacture of a medicament in treating a cancer patient selected as likely to experience a

15 longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11 T>A;
- b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
- 20 c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,
- in a sample isolated from the patient.

[0290] Also provided is a therapy comprising, or alternatively consisting essentially of, or yet further consisting of, a platinum drug and a mitotic inhibitor for use in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the

25 therapy, based on the presence of at least one genotype of the group:

- a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11 T>A;
- b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
- c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,
- 30 in a sample isolated from the patient.

[0291] For the above noted methods, the patient can be selected by determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A.

5 [0292] Also provided is a method for treating a cancer patient selected as less likely to experience a side effect from receiving a, based on the presence of a genotype of (G/G or G/T) for WNK1 rs110644560 G>T in a sample from the patient, comprising, or alternatively consisting essentially of, or yet further consisting of, administering the therapy to the cancer patient, thereby treating the patient.

10 [0293] Further provided is the use of a chemotherapy for the manufacture of a medicament in treating a cancer patient selected as less likely to experience a side effect from receiving a, based on the presence of a genotype of (G/G or G/T) for WNK1 rs110644560 G>T in a sample isolated from the patient.

15 [0294] Yet further provided is a chemotherapy for use in treating a cancer patient selected as less likely to experience a side effect from receiving a, based on the presence of a genotype of (G/G or G/T) for WNK1 rs110644560 G>T in a sample isolated from the patient.

[0295] For the above methods, the patient can be selected by determining a genotype of a cell or tissue sample isolated from the patient for a WNK1 rs110644560 G>T polymorphism.

20 [0296] In one aspect, the side effect is hypertension.

[0297] For the above therapies, uses and compositions, the chemotherapy is an anti-VEGF-based therapy or a therapy comprising, or alternatively consisting essentially of, or yet further consisting of, a platinum drug and a mitotic inhibitor. In another aspect, the chemotherapy comprises, or alternatively consisting essentially of, or yet further consisting of, administration of carboplatin or an equivalent thereof in combination with paclitaxel or an equivalent thereof. In a yet further aspect, the chemotherapy comprises, or alternatively consisting essentially of, or yet further consisting of, administration of bevacizumab or an equivalent thereof in combination with carboplatin or an equivalent thereof and paclitaxel or an equivalent thereof.

25

[0298] For the above therapies, uses or compositions, the cancer patient is suffering from at least one cancer of the type of the group: metastatic or non-metastatic rectal cancer, metastatic or non-metastatic colon cancer, metastatic or non-metastatic colorectal cancer, non-small cell lung cancer (NSCLC), metastatic breast cancer, non-metastatic breast cancer, renal cell carcinoma, glioblastoma multiforme, ovarian cancer, hormone-refractory prostate cancer, non-metastatic unresectable liver cancer, head and neck cancer, advanced Kaposi's sarcoma, or metastatic or unresectable locally advanced pancreatic cancer. In a further aspect, the cancer patient is suffering from lung cancer. In a yet further aspect, the lung cancer is non-small cell lung cancer.

[0299] The isolated samples can comprise, or alternatively consisting essentially of, or yet further consisting of, at least one of a tumor cell, a normal cell adjacent to a tumor, a normal cell corresponding to the tumor tissue type, a blood cell, a peripheral blood lymphocyte, or combinations thereof. The sample can comprise, or alternatively consisting essentially of, or yet further consisting of, at least one of a fixed tissue, a frozen tissue, a biopsy tissue, a resection tissue, a microdissected tissue, or combinations thereof.

[0300] In some embodiments, the cancer patients may receive an anti-VEGF-based therapy, which anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of administration of an anti-VEGF antibody, a VEGF inhibitor, or equivalents thereof. In one aspect, the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of, administration of bevacizumab or an equivalent thereof. In another aspect, the anti-VEGF-based therapy further comprises, or alternatively consists essentially of, or yet further consists of, administration of a platinum drug. In one aspect, the platinum drug is carboplatin or an equivalent thereof. In another aspect, the anti-VEGF-based therapy further comprises, or alternatively consists essentially of, or yet further consists of, administration of a mitotic inhibitor. In one aspect, the mitotic inhibitor is paclitaxel or an equivalent thereof. In some embodiments, the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of administration of an anti-VEGF antibody in combination with a platinum drug and a mitotic inhibitor. In one aspect, the anti-VEGF-based therapy comprises, or alternatively consists essentially of, or yet further consists of, administration of bevacizumab or an equivalent thereof in combination with carboplatin or an equivalent thereof, and paclitaxel or an

equivalent thereof. In one aspect, the administration of the anti-VEGF antibody, the platinum drug or the mitotic inhibitor is concurrent or sequential.

[0301] In some embodiments, the cancer patients may receive a platinum drug and mitotic inhibitor combination therapy, which platinum drug and mitotic inhibitor combination
5 therapy comprises, or alternatively consists essentially of, or yet further consists of, administration of a platinum drug and a mitotic inhibitor. In one aspect, the platinum drug is carboplatin or an equivalent thereof. In one aspect, the mitotic inhibitor is paclitaxel or an equivalent thereof. In some embodiments, the administration of the platinum drug and mitotic inhibitor is concurrent or sequential.

10 [0302] In some embodiments of these treatments, the cancer patient is suffering from at least one cancer of the type of the group: metastatic or non-metastatic rectal cancer, metastatic or non-metastatic colon cancer, metastatic or non-metastatic colorectal cancer, non-small cell lung cancer (NSCLC), metastatic breast cancer, non-metastatic breast cancer, renal cell carcinoma, glioblastoma multiforme, ovarian cancer, hormone-refractory prostate
15 cancer, non-metastatic unresectable liver cancer, head and neck cancer, advanced Kaposi's sarcoma, or metastatic or unresectable locally advanced pancreatic cancer. In one aspect, the cancer patient is suffering from lung cancer. In one aspect, the lung cancer is non-small cell lung cancer.

[0303] The formulation comprising the necessary chemotherapy or biological equivalent
20 thereof is further provided herein. The formulation can further comprise one or more preservatives or stabilizers. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1,
25 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-2% m-cresol (e.g., 0.2, 0.3, 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1, 1.5, 1.9, 2.0, 2.5%), 0.001-0.5% thimerosal (e.g., 0.005, 0.01), 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9, 1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075,
30 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, and 1.0%).

[0304] The chemotherapeutic agents or drugs can be administered as a composition. A “composition” typically intends a combination of the active agent and another carrier, e.g., compound or composition, inert (for example, a detectable agent or label) or active, such as an adjuvant, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like and include pharmaceutically acceptable carriers. Carriers also include pharmaceutical excipients and additives proteins, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. Carbohydrate excipients are also intended within the scope of this invention, examples of which include but are not limited to monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol) and myoinositol.

[0305] The term carrier further includes a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Additional carriers include polymeric excipients/additives such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrans (e.g., cyclodextrins, such as 2-hydroxypropyl- β -cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as “TWEEN 20” and “TWEEN 80”), lipids (e.g., phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

[0306] As used herein, the term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents. The compositions also can include stabilizers and preservatives and any of the
5 above noted carriers with the additional proviso that they be acceptable for use *in vivo*. For examples of carriers, stabilizers and adjuvants, see Martin REMINGTON'S PHARM. SCI., 15th Ed. (Mack Publ. Co., Easton (1975) and Williams & Williams, (1995), and in the "PHYSICIAN'S DESK REFERENCE", 52nd ed., Medical Economics, Montvale, N.J. (1998).

10 [0307] Many combination chemotherapeutic regimens are known to the art, such as combinations of platinum compounds and taxanes, e.g. carboplatin/paclitaxel, capecitabine/docetaxel, the "Cooper regimen", fluorouracil-levamisole, fluorouracil-leucovorin, fluorouracil/oxaliplatin, methotrexate-leucovorin, and the like.

[0308] Combinations of chemotherapies and molecular targeted therapies, biologic
15 therapies, and radiation therapies are also well known to the art; including therapies such as trastuzumab plus paclitaxel, alone or in further combination with platinum compounds such as oxaliplatin, for certain breast cancers, and many other such regimens for other cancers; and the "Dublin regimen" 5-fluorouracil IV over 16 hours on days 1-5 and 75 mg/m² cisplatin IV or oxaliplatin over 8 hours on day 7, with repetition at 6 weeks, in combination
20 with 40 Gy radiotherapy in 15 fractions over the first 3 weeks) and the "Michigan regimen" (fluorouracil plus cisplatin or oxaliplatin plus vinblastine plus radiotherapy), both for esophageal cancer, and many other such regimens for other cancers, including colorectal cancer.

[0309] In another aspect of the invention, the method for treating a patient comprises, or
25 alternatively consists essentially of, or yet further consists of surgical resection of a metastatic or non-metastatic solid malignant tumor and, in some aspects, in combination with radiation. Methods for treating said tumors derived from a gastrointestinal cancer, e.g., metastatic or non-metastatic rectal cancer, metastatic or non-metastatic colon cancer, metastatic or non-metastatic colorectal cancer, gastric cancer, esophageal cancer, stage II
30 colon cancer, stage II rectal cancer or stage III rectal cancer by surgical resection and/or radiation are known to one skilled in the art. Guidelines describing methods for treatment

by surgical resection and/or radiation can be found at the National Comprehensive Cancer Network's web site, nccn.org, last accessed on May 27, 2008.

[0310] The invention provides an article of manufacture, comprising packaging material and at least one vial comprising a solution of the chemotherapy as described herein and/or
5 or at least one antibody or its biological equivalent with the prescribed buffers and/or preservatives, optionally in an aqueous diluent, wherein said packaging material comprises a label that indicates that such solution can be held over a period of 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further comprises an article of manufacture, comprising packaging material, a first vial comprising the
10 chemotherapy and/or at least one lyophilized antibody or its biological equivalent and a second vial comprising an aqueous diluent of prescribed buffer or preservative, wherein said packaging material comprises a label that instructs a patient to reconstitute the therapeutic in the aqueous diluent to form a solution that can be held over a period of twenty-four hours or greater.

[0311] When an antibody is administered, the antibody or equivalent thereof is prepared
15 to a concentration includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 µg/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or
20 osmotic or micro pump methods.

[0312] Chemotherapeutic formulations of the present invention can be prepared by a process which comprises mixing at least one antibody or biological equivalent and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like),
25 benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing of the antibody and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. For example, a measured amount of at least one antibody in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide the
30 antibody and preservative at the desired concentrations. Variations of this process would be recognized by one of skill in the art, e.g., the order the components are added, whether

additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

[0313] The compositions and formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized antibody that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available. Recognized devices comprising these single vial systems include those pen-injector devices for delivery of a solution such as BD Pens, BD Autojectore, Humaject® NovoPen®, B-D®Pen, AutoPen®, and OptiPen®, GenotropinPen®, Genotronorm Pen®, Humatro Pen®, Reco-Pen®, Roferon Pen®, Biojector®, iject®, J-tip Needle-Free Injector®, Intraject®, Medi-Ject®, e.g., as made or developed by Becton Dickenson (Franklin Lakes, N.J. available at bectondickenson.com), Disetronic (Burgdorf, Switzerland, available at disetronic.com; Bioject, Portland, Oregon (available at bioject.com); National Medical Products, Weston Medical (Peterborough, UK, available at weston-medical.com), Medi-Ject Corp (Minneapolis, Minn., available at mediject.com).

[0314] Various delivery systems are known and can be used to administer a chemotherapeutic agent of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, expression by recombinant cells, receptor-mediated endocytosis. See e.g., Wu and Wu (1987) J. Biol. Chem. **262**:4429-4432 for construction of a therapeutic nucleic acid as part of a retroviral or other vector, etc. Methods of delivery include but are not limited to intra-arterial, intra-muscular, intravenous, intranasal and oral routes. In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, by injection or by means of a catheter.

[0315] The agents identified herein as effective for their intended purpose can be administered to subjects or individuals identified by the methods herein as suitable for the therapy. Therapeutic amounts can be empirically determined and will vary with the pathology being treated, the subject being treated and the efficacy and toxicity of the agent.

[0316] Also provided is a medicament or a therapy comprising an effective amount of a chemotherapeutic as described herein for treatment of a human cancer patient having high or low gene expression or the polymorphism of the gene of interest as identified in the experimental examples.

- 5 [0317] Methods of administering pharmaceutical compositions are well known to those of ordinary skill in the art and include, but are not limited to, oral, microinjection, intravenous or parenteral administration. The compositions are intended for topical, oral, or local administration as well as intravenously, subcutaneously, or intramuscularly. Administration can be effected continuously or intermittently throughout the course of the treatment.
- 10 Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the cancer being treated and the patient, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

Kits and Panels

- 15 [0318] Also provided is a kit for use in identifying a cancer patient likely to experience a longer or shorter overall survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, suitable primers or probes or a microarray for screening at least two polymorphisms of the group ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A, and instructions for use therein.
- 20 [0319] Also provided is a kit for use in identifying a cancer patient likely to experience a longer or shorter overall survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, suitable primers or probes or a microarray for screening at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, GSTP1 A105G, or
- 25 WNK1 rs11064560 T>G, and instructions for use therein.

[0320] Also provided is a kit for use in identifying a cancer patient likely to experience a longer or shorter progression free survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, suitable primers or probes or a microarray for screening at least two polymorphisms of the group

VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C, and instructions for use therein.

[0321] Also provided is a kit for use in identifying a cancer patient likely to experience a longer or shorter progression free survival from receiving an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, suitable
5 primers or probes or a microarray for screening at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF G-634C, VEGF C-1498T, CXCR2 C+785T, or WNK1 rs11064560 T>G, and instructions for use therein.

[0322] Also provided is a kit for use in identifying a cancer patient more or less likely to
10 respond to an anti-VEGF-based therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, determining a genotype of a cell or tissue sample isolated from the patient for two polymorphisms of the group COX2 G-765C or WNK1 rs11064560 T>G, and instructions for use therein.

[0323] Also provided is a A kit for use in identifying a cancer patient likely to experience
15 a longer or shorter overall survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, suitable primers or probes or a microarray for screening at least two polymorphisms of the group VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A, and instructions for use therein.

[0324] Also provided is a kit for use in identifying a cancer patient likely to experience a
20 longer or shorter overall survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, suitable primers or probes or a microarray for screening at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR
25 exon 11 T>A, VEGF C-1498T, VEGF G-1154A, EGF A+61G, or COX2 G-765C, and instructions for use therein.

[0325] Also provided is a kit for use in identifying a cancer patient likely to experience a longer or shorter progression free survival from receiving a platinum drug and mitotic inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet
30 further consisting of, suitable primers or probes or a microarray for screening at least two

polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A, and instructions for use therein.

[0326] Also provided is a kit for use in identifying a cancer patient likely to experience a longer or shorter progression free survival from receiving a platinum drug and mitotic
5 inhibitor combination therapy, comprising, or alternatively consisting essentially of, or yet further consisting of, suitable primers or probes or a microarray for screening at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, EGF A+61G, and GSTP1 A105G, and instructions for use therein.

[0327] In an embodiment, the invention provides a kit for determining whether a subject
10 is likely responsive to cancer treatment or alternatively one of various treatment options. The kits contain one or more of the compositions described above and instructions for use. As an example only, the invention also provides kits for determining response to cancer treatment containing a first and a second oligonucleotide specific for the polymorphic region of the gene. Oligonucleotides "specific for" the gene of interest bind either to the
15 gene of interest or bind adjacent to the gene of interest. For oligonucleotides that are to be used as primers for amplification, primers are adjacent if they are sufficiently close to be used to produce a polynucleotide comprising, or alternatively consisting essentially of, or yet further consisting of, the gene of interest. In one embodiment, oligonucleotides are adjacent if they bind within about 1-2 kb, and preferably less than 1 kb from the gene of
20 interest. Specific oligonucleotides are capable of hybridizing to a sequence, and under suitable conditions will not bind to a sequence differing by a single nucleotide.

[0328] The kit can comprise at least one probe or primer which is capable of specifically hybridizing to the gene of interest and instructions for use. The kits preferably comprise at least one of the above described nucleic acids. Preferred kits for amplifying at least a
25 portion of the gene of interest comprise two primers, at least one of which is capable of hybridizing to the allelic variant sequence. Such kits are suitable for detection of genotype by, for example, fluorescence detection, by electrochemical detection, or by other detection.

[0329] Oligonucleotides, whether used as probes or primers, contained in a kit can be detectably labeled. Labels can be detected either directly, for example for fluorescent
30 labels, or indirectly. Indirect detection can include any detection method known to one of skill in the art, including biotin-avidin interactions, antibody binding and the like.

Fluorescently labeled oligonucleotides also can contain a quenching molecule.

Oligonucleotides can be bound to a surface. In one embodiment, the preferred surface is silica or glass. In another embodiment, the surface is a metal electrode.

5 **[0330]** Yet other kits of the invention comprise at least one reagent necessary to perform the assay. For example, the kit can comprise an enzyme. Alternatively the kit can comprise a buffer or any other necessary reagent.

10 **[0331]** Conditions for incubating a nucleic acid probe with a test sample depend on the format employed in the assay, the detection methods used, and the type and nature of the nucleic acid probe used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification or immunological assay formats can readily be adapted to employ the nucleic acid probes for use in the present invention. Examples of such assays can be found in Chard, T. (1986) AN INTRODUCTION TO RADIOIMMUNOASSAY AND RELATED TECHNIQUES Elsevier Science Publishers, Amsterdam, The Netherlands; Bullock, G.R. et al., TECHNIQUES IN
15 IMMUNOCYTOCHEMISTRY Academic Press, Orlando, FL Vol. 1 (1982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P. (1985) PRACTICE AND THEORY OF IMMUNOASSAYS: LABORATORY TECHNIQUES IN BIOCHEMISTRY AND MOLECULAR BIOLOGY, Elsevier Science Publishers, Amsterdam, The Netherlands.

20 **[0332]** The test samples used in the diagnostic kits include cells, protein or membrane extracts of cells, or biological fluids such as sputum, blood, serum, plasma, or urine. The test samples may also be a tumor cell, a normal cell adjacent to a tumor, a normal cell corresponding to the tumor tissue type, a blood cell, a peripheral blood lymphocyte, or combinations thereof. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as
25 the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are known in the art and can be readily adapted in order to obtain a sample which is compatible with the system utilized.

30 **[0333]** The kits can include all or some of the positive controls, negative controls, reagents, primers, sequencing markers, probes and antibodies described herein for determining the subject's genotype in the polymorphic region of the gene of interest.

[0334] As amenable, these suggested kit components may be packaged in a manner customary for use by those of skill in the art. For example, these suggested kit components may be provided in solution or as a liquid dispersion or the like.

5 [0335] The suggested kits may further comprise a pharmaceutically effective amount of a therapy and optionally instructions for use therein. Such pharmaceutically effective amount of therapies are described supra.

[0336] Also provided is a prognostic panel of genetic markers comprising, or alternatively consisting essentially of, or yet further consisting of, a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the
10 group: ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A.

[0337] Further provided is a prognostic panel of genetic markers comprising, or alternatively consisting essentially of, or yet further consisting of, a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A,
15 GSTP1 A105G, or WNK1 rs11064560 T>G.

[0338] Also provided is a prognostic panel of genetic markers comprising, or alternatively consisting essentially of, or yet further consisting of, a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or
20 COX G-765C.

[0339] Also provided is a prognostic panel of genetic markers comprising, or alternatively consisting essentially of, or yet further consisting of, a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF G-634C, VEGF C-1498T, CXCR2
25 C+785T, or WNK1 rs11064560 T>G.

[0340] Also provided is a prognostic panel of genetic markers comprising, or alternatively consisting essentially of, or yet further consisting of, a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: COX2 G-765C or WNK1 rs11064560 T>G.

[0341] Also provided is a prognostic panel of genetic markers comprising, or alternatively consisting essentially of, or yet further consisting of, a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A.

[0342] Also provided is a prognostic panel of genetic markers comprising, or alternatively consisting essentially of, or yet further consisting of, a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF C-1498T, VEGF G-1154A, EGF A+61G, or COX2 G-765C.

[0343] This invention also provides a prognostic panel of genetic markers comprising, or alternatively consisting essentially of, or yet further consisting of, a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A.

[0344] This invention further provides a prognostic panel of genetic markers comprising, or alternatively consisting essentially of, or yet further consisting of, a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ERCC1 3'UTR C>A, KDR exon 11 T>A, EGF A+61G, and GSTP1 A105G.

[0345] In one aspect of each of the above panels, the primer or probe is attached to a microarray. In another aspect, the primer or probe is detectably labeled.

Other Uses for the Nucleic Acids of the Invention

[0346] The identification of the polymorphic region or the expression level of the gene of interest can also be useful for identifying an individual among other individuals from the same species. For example, DNA sequences can be used as a fingerprint for detection of different individuals within the same species. Thompson, J. S. and Thompson, eds., (1991) GENETICS IN MEDICINE, W B Saunders Co., Philadelphia, Pa. This is useful, e.g., in forensic studies.

[0347] The invention now being generally described, it will be more readily understood by reference to the following example which is included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

5

EXPERIMENTAL EXAMPLES

Example 1

[0348] **Background:** E4599 was a randomized phase III study which demonstrated a survival advantage in advanced NSCLC patients treated with bevacizumab (bev) + carboplatin/paclitaxel (BPC) versus carboplatin/paclitaxel alone (PC). This study was to test the whether SNPs involved in angiogenesis pathway (VEGF, EGF, EGFR, IL-8, KDR, ICAM1, FGFR4), DNA repair pathway (ERCC1, XPD, XRCC1, GSTP1) & WNK1 may predict clinical outcome in a subset of patients enrolled on E4599.

[0349] **Methods:** Of 878 patients enrolled, samples from 146 patients were available for the current pharmacogenetic study & 133 of the samples (67 PC, 66 BPC) came from eligible patients. PCR-RFLP assays were performed on genomic DNA extracted from sera of patients. The Kaplan-Meier method was used to estimate time-to-event distributions. Multivariable Cox models adjusted for gender, PS, stage, adrenal, liver & bone mets were separately fitted for each SNP to obtain estimates of hazard ratios (HR).

[0350] **Results:** Median OS for the 133 patients was 10.3 mos (8.2-15.6) for PC & 13.0 mos (10.2-16.6) for BPC. Median PFS was 4.6 mos (3.6-5.6) for PC & 6.5 mos (5.4-8.3) for BPC. Patients with mutant homozygote CC genotype for ICAM1 T469C had significantly higher tumor response rate (39%) than heterozygote CT (13%) & homozygote TT (20%) genotype (Fisher's test, $p=0.04$). Tests for whether treatment effect differs by genotype via interaction terms in the Cox models were statistically significant ($p<0.05$) for VEGF G-634C, ICAM1 T469C & WNK1-rs11064560 for OS, and for ICAM1 T469C, EGF A+61G & CXCR2 C785T for PFS. Although exploratory, these preliminary results suggest germline SNPs in angiogenesis pathway may predict response, PFS & OS in NSCLC patients treated with BPC.

Example 2

Multivariate statistical analysis of data from Example 1

[0351] E4599 was a randomized phase III study of whether or not the addition of bevacizumab (BPC) to carboplatin/paclitaxel (PC) improves overall survival for patients with advanced stage non-small cell lung cancer. The first objective of this project is to identify germline polymorphisms associated with response, progression-free survival and overall survival in patients with NSCLC treated on this study. It is also of interest to study an association with certain toxicities.

[0352] In this study, a total of 146 samples were available, and 133 of these samples came from patients who met all eligibility criteria for the study. Among the 133 samples represented in this analysis, 67 samples came from patients on PC, and the other 66 came from patients randomized to BPC.

[0353] For the analysis of response data, response was dichotomized into responders defined as those having achieved a best response of partial or complete response per RECIST criteria, and non-responders; note that response can only be assessed on those patients who presented with measurable disease. Specifically, 124 (93%) out of the 133 eligible patients had measurable disease at baseline. A Fisher exact test with a 2-sided 5% type I error rate was used to detect an association between response and each of the polymorphism genotypes. This was done overall and within each of the treatment arms.

[0354] Overall survival was defined as the time from randomization to death from any cause, censored at the last date of followup. Progression-free survival (PFS) was defined as the time from randomization to documented progression per RECIST or death, censored at the last date of evaluation. The Kaplan-Meier method was used to estimate the time-to-event distributions and log-rank tests were used to test for differences in time-to-event endpoints. Cox proportional hazards regression models were used to estimate hazard ratios. Multivariable Cox regression models were fitted adjusting for treatment arm, ECOG performance status (0 vs. 1), stage (IIIB/IV vs. recurrent), histology (adenocarcinoma vs. other) weight loss (<10% vs. ≥10%), gender, and age (<70 vs. ≥ 70).

[0355] All p-values are two-sided. Analyses of polymorphisms used all patients with genotype data for that polymorphism. No adjustments were made for multiple comparisons due to the exploratory nature of this analysis.

Results

- 5 [0356] Table 1 displays the distribution of the polymorphisms overall and by treatment arm. There was an imbalance of ERCC1-118 by treatment arm ($p=0.002$). These frequencies were tabulated for each of the baseline variables of interest: ECOG performance status (0 vs. 1), stage (IIIB/IV vs. recurrent), histology (adenocarcinoma vs. other) weight loss ($<10\%$ vs. $\geq 10\%$), gender, and age (<70 vs. ≥ 70). Results are not displayed in this
- 10 report (to shorten the report length) but they are available upon request.

Table 1. Distribution of polymorphisms by treatment arm.

				Eligible Patients		Eligible Patients	
		All Eligible		Carbo/Taxol		Carbo/Taxol/Bev	
Polymorphism	Genotype	n	%	n	%	n	%
VEGF C+936T	CC	111	0.841	57	0.851	54	0.831
	CT or TT	21	0.159	10	0.149	11	0.169
VEGF G-634C	GG	70	0.538	33	0.493	37	0.587
	GC	41	0.315	26	0.388	15	0.238
	CC	19	0.146	8	0.119	11	0.175
VEGF C-1498T	CC	40	0.310	18	0.273	22	0.349
	CT	47	0.364	25	0.379	22	0.349
	TT	42	0.326	23	0.348	19	0.302
VEGF G-1154A	GG	46	0.390	21	0.350	25	0.431
	AG	31	0.263	20	0.333	11	0.190
	AA	41	0.347	19	0.317	22	0.379
ICAM1 T469C	TT	46	0.357	23	0.343	23	0.371
	CT	57	0.442	33	0.493	24	0.387
	CC	26	0.202	11	0.164	15	0.242
FGFR4 G388A	GG	56	0.463	25	0.397	31	0.534
	AG	53	0.438	33	0.524	20	0.345
	AA	12	0.099	5	0.079	7	0.121

EGF A+61G	AA	27	0.211	14	0.212	13	0.210
	AG	62	0.484	32	0.485	30	0.484
	GG	39	0.305	20	0.303	19	0.306
EGFR G497A	GG	21	0.163	11	0.164	10	0.161
	AG	67	0.519	37	0.552	30	0.484
	AA	41	0.318	19	0.284	22	0.355
IL8 T-251A	TT	72	0.550	32	0.478	40	0.625
	AT or AA	59	0.450	35	0.522	24	0.375
CXCR2 C+785T	CC	27	0.206	16	0.239	11	0.172
	CT	56	0.427	28	0.418	28	0.438
	TT	48	0.366	23	0.343	25	0.391
ERCC1 C118T	CC	39	0.300	19	0.288	20	0.313
	CT	56	0.431	37	0.561	19	0.297
	TT	35	0.269	10	0.152	25	0.391
ERCC1 3'UTR C/A	CC	67	0.519	31	0.463	36	0.581
	AC	49	0.380	27	0.403	22	0.355
	AA	13	0.101	9	0.134	4	0.065
XPD A751C	AA	43	0.331	16	0.239	27	0.429
	AC	68	0.523	41	0.612	27	0.429
	CC	19	0.146	10	0.149	9	0.143
XPD C156A	CC	56	0.441	29	0.433	27	0.450
	AC	51	0.402	29	0.433	22	0.367
	AA	20	0.157	9	0.134	11	0.183
XRCC1 G-399A	GG	52	0.397	31	0.463	21	0.328
	AG	69	0.527	33	0.493	36	0.563
	AA	10	0.076	3	0.045	7	0.109
COX2 G-765C	GG	60	0.488	34	0.540	26	0.433
	CG	47	0.382	24	0.381	23	0.383
	CC	16	0.130	5	0.079	11	0.183
GSTP1 A105G	AA	66	0.508	40	0.597	26	0.413
	AG	51	0.392	22	0.328	29	0.460
	GG	13	0.100	5	0.075	8	0.127
KDR EXON 11 T/A	TT	57	0.432	31	0.463	26	0.400
	TA or AA	75	0.568	36	0.537	39	0.600

WVK1rs11064560							
T/G	TT	53	0.405	29	0.433	24	0.375
	GT	61	0.466	28	0.418	33	0.516
	GG	17	0.130	10	0.149	7	0.109
WVK1rs2158501							
G/A	GG	44	0.352	22	0.333	22	0.373
	AG	47	0.376	23	0.348	24	0.407
	AA	34	0.272	21	0.318	13	0.220

Overall Survival

[0357] With regards to overall survival, pertinent results are as follows:

- Patients with the mutant homozygote (TT) for VEGF936 have 7.048 times the risk of death compared to those with the WT homozygote (CC), $p=0.058$. This result did not hold when Cox models were fitted separately to each treatment arm.
- Those with the mutant heterozygote for ICAM1-469 had 1.573 times the risk of death when compared to those with the WT homozygote ($p=0.029$).
- For IL8-251, patients with the mutant homozygote had 9.411 times the risk of death when compared to those with the WT homozygote ($p=0.003$).
- For CXCR2-785, both mutant alleles had significantly lower risk of death compared to the WT homozygote group.
- For ERCC1-3'UTR, those with mutant heterozygote had a lower risk of death than the WT homozygotes ($p=0.027$). A similar result holds for KDR ($p=0.054$).
- Among patients on the PC arm, those with the mutant homozygote (TT) for VEGF1498 had 0.454 times the risk of death compared to those with the WT homozygote, $p=0.017$. A similar relationship on the PC arm holds in relation to EGF61 ($p=0.028$) and COX2-765 ($p=0.054$). Those with the mutant homozygote for VEGF1154 had higher risk of death ($p=0.024$).
- Among those on the BPC arm, patients with the mutant homozygote for IL8-251 had 13.685 times the risk of death when compared to those with the mutant homozygote ($p=0.02$). A similar relationship holds for KDR ($p=0.012$) and WVK1-11064560 ($p=0.012$). For two genes, the mutant heterozygotes had a significantly lower risk of

death compared to the WT homozygotes:ERCC1-3'UTR ($p=0.054$) and GSTP1-105 ($p=0.035$).

[0358] Hazard ratios, 95% confidence intervals and p-values are provided in Table 2.

Table 2. Overall Survival Hazard Ratios

Polymorphism	Genotype	n	ELIGIBLE Patients				Carboplatin/Paclitaxel				Carbo/Paclitaxel/Bevacizumab		
			HR	95% CI	p-value		HR	95% CI	p-value		HR	95% CI	p-value
VEGF	C+936T	111	ref	*	*	ref	*	*	*	ref	*	*	*
VEGF G-634C	CC or TT	21	0.863	0.523	1.426	0.566	0.82	0.401	1.678	0.588	0.862	0.423	1.757
VEGF G-634C	GG	70	ref	*	*	ref	*	*	*	ref	*	*	*
VEGF G-634C	GC	41	1.062	0.708	1.592	0.771	0.608	0.353	1.045	0.072	1.839	0.971	3.485
VEGF G-634C	CC	19	1.076	0.641	1.806	0.783	0.697	0.318	1.528	0.368	1.406	0.698	2.834

VEGF C-1498T	CC	40	ref	*	*	*	*	ref	*	*	*	*	ref	*	*	*	*	*
	CT	47		1.218	0.784	1.893	0.381		0.74	5	0.3	1.40		1.4	0.7	2.80	3	0.213
	TT	42		0.784	0.499	1.231	0.291		0.45	4	0.2	0.86		0.9	0.5			0.99
	GG	46	ref	*	*	*	*	ref	*	*	*	*		*	*	*	*	*
	AG	31		1.173	0.729	1.888	0.512		1.22	6	0.6	2.30		1.0	0.4	2.18	5	0.99
	AA	41		1.345	0.869	2.08	0.184		2.11	1	0.6	4.03		1.0	0.5	1.91	9	0.863
ICAM1 T469C	TT	46	ref	*	*	*	*	ref	*	*	*	*		*	*	*	*	*
	CT	57		1.573	1.048	2.362	0.029		1.46	2	0.8	2.52		1.6	0.8	3.02	7	0.118
	AA	26		1.096	0.663	1.811	0.722		0.61	6	0.2	1.33		1.7	0.8	3.53	6	0.104
	GG	56	ref	*	*	*	*	ref	*	*	*	*		*	*	*	*	*
FGFR4 G388A				0.908	0.616	1.338	0.627		0.68	5	0.4	1.16		1.1	0.6	2.01	4	0.723
	AG	53																
	AA	12		0.802	0.418	1.541	0.509		0.66	7	0.2	1.94		0.9	0.4	2.15	4	0.882

EGF A+61G	AA	27	ref	*	*	*	*	*	*	*	*	*	*	ref	*	*	*	*	*
	AG	62		0.922	0.577	1.474	0.735		0.85	0.4	1.61	8	54		0.9	0.4	1.93	2	0.903
	GG	39		0.722	0.433	1.204	0.212		0.44	0.2	0.91	9	2		1.0	0.4			0.893
EGFR G497A	GG	21	ref	*	*	*	*	*	ref	*	*	*	*	ref	*	*	*	*	*
	AG	67		1.118	0.669	1.868	0.67		1.15	0.5	2.29	9	84		1.0	0.4	2.42	8	0.817
	AA	41		0.891	0.512	1.55	0.683		0.89	0.4	1.91	7	19		0.9	0.4	2.14	8	0.876
IL8 T-251A	TT	72	ref	*	*	*	*	*	ref	*	*	*	*	ref	*	*	*	*	*
	AT or AA	59		1.005	0.702	1.44	0.977		1.27	0.7	2.09		71		0.7	0.4	1.26		0.258
CXCR2 C+785T	CC	27	ref	*	*	*	*	*	ref	*	*	*	*	ref	*	*	*	*	*
	CT	56		0.593	0.369	0.953	0.031		0.59	0.3	1.12		11		0.6	0.3	1.31	8	0.228
	TT	48		0.588	0.364	0.951	0.03		0.67	0.3	1.29		5		0.5	0.2	1.16	9	0.125

ERCC1 C118T	CC	39	ref	*	*	*	*	*	*	*	*	ref	*	*	*	*	*	*	*
	CT	56		1.013	0.661	1.553	0.952		0.97	0.5	1.73		0.8	0.4	1.75		0.748		
	TT	35		1.442	0.902	2.308	0.127		1.22	0.5	2.67		1.7	0.9	3.25		0.072		
ERCC1 3'UTR C/A	CC	67	ref	*	*	*	*			*	*	ref	*	*	*		*		
	AC	49		0.644	0.436	0.951	0.027		0.70	0.4	1.20		0.5	0.3	1.00		0.054		
	AA	13		0.91	0.5	1.659	0.759		0.82	0.3	1.73		0.9	0.3			0.924		
XPD A751C	AA	43	ref	*	*	*	*			*	*	ref	*	*	*		*		
	AC	68		0.99	0.665	1.475	0.961		1.19	0.6	2.17		0.7	0.4	1.30		0.297		
	CC	19		1.472	0.847	2.56	0.171		2.18	0.9	4.94		1.1	0.5	2.38		0.806		
XPD C156A	CC	56	ref	*	*	*	*			*	*	ref	*	*	*		*		
	AC	51		0.939	0.633	1.393	0.756		1.06	0.6	1.80		0.8	0.4	1.46		0.476		
	AA	20		0.957	0.565	1.622	0.87		0.77	0.3	1.71		1.1	0.5	2.37		0.685		

XRCC1 G-399A	GG	52	ref	*	*	*	*	*	*	*	*	ref	*	*	*	*	*	*
				1.089	0.748	1.586	0.656			1.1	0.6		1.1	0.6	2.04			
	AG	69											45	41	4	0.648		
COX2 G-765C	AA	10		0.984	0.482	2.008	0.964			0.96	0.2		3	91	3.19	0.951		
	GG	60	ref	*	*	*	*	*	*	*	*	ref	*	*	*	*	*	*
	CG	47		0.867	0.583	1.288	0.479			0.61	0.3		7	58	3	0.082		
	CC	16		0.699	0.393	1.243	0.223			0.37	0.1		7	4	7	0.054		
GSTP1 A105G	AA	66	ref	*	*	*	*	*	*	*	*	ref	*	*	*	*	*	*
										1.26	0.7		8	4	4	0.388		
	AG	51		0.78	0.533	1.143	0.203											
KDR EXON 11 T/A	GG	13		0.86	0.463	1.598	0.633			0.88	0.3		5	44	1	0.801		
	TT	57	ref	*	*	*	*	*	*	*	*	ref	*	*	*	*	*	*
	TA or AA	75		0.7	0.487	1.007	0.054			0.64	0.3		2	86	6	0.087		

WNK1rs1106	TT	53	ref	*	*	*	*	ref	*	*	*	ref	*	*	*	*
	GT	61		0.901	0.615	1.32	0.594		1.00	0.5	1.71		0.8	0.5	1.52	
	GG	17		1.096	0.624	1.927	0.749		0.63	0.2	1.35		3.1	1.2	7.88	0.636
WNK1rs2158	GG	44	ref	*	*	*	*	ref	*	*	*	ref	*	*	*	*
	AG	47		1.25	0.815	1.915	0.307		1.14	0.6	2.08		1.3	0.7	2.52	0.313
	AA	34		1.11	0.696	1.771	0.661		1.17	0.6	2.18		0.9	0.4	1.91	0.818

Progression-Free Survival

[0359] With regards to PFS, pertinent results are as follows:

- Overall, those with the mutant homozygote saw significantly higher risk of progression/death when compared to the WT homozygote for the following genes: VEGF936 (p=0.001) and IL8-251 (p=0.007).
- Overall, those with the mutant heterozygote saw significantly lower risk of progression/death when compared to the WT homozygote for the following genes: ERCC1-3'UTR (p=0.056) and KDR (p=0.037).

- Among those on the PC arm only, those with the mutant homozygote saw significantly different risk of progression/death when compared to the WT homozygote for the following genes: VEGF936 (p=0.004) and EGF-61 (p=0.011). When we compared the mutant heterozygote to the WT homozygotes, the following genes had notable results: ERCC1-3'UTR, GSTP-105, and KDR.
- Among those on the BPC arm, those with the mutant homozygote saw significantly different risk of progression/death when compared to the WT homozygote for the following genes: IL8-251 (p=0.019), CXCR-785 (p=0.046), KDR (p=0.039) and WNK1-11064560 (p=0.034). When we compared the mutant heterozygote to the WT homozygotes, the following genes had notable results: VEGF634 and VEGF1498.

[0360] Hazard ratios, 95% confidence intervals and p-values are provided in Table 3.

Table 3. PFS Hazard Ratios

Polymorphism	Genotype	n	Eligible Patients			Carboplatin/Paclitaxel			Carbo/Paclitaxel/Bevacizumab			
			HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	
VEGF C+936T	CC	111	ref	*	*	ref	*	*	*	*	*	*
	CT or TT	21	1.5 16	0.933 3	2.46 0.093	1.46 5	0.717 2.996	0.295	1.68 8	0.86 6	3.2 88	0.124

VEGF G-634C	GG	70	ref	*	*	*	*	ref	*	*	*	ref	*	*	*	*	*
				1.3					0.85								
	GC	41		61	0.916	2	0.128		1	0.504	1.438	0.547		1.85	0.99	3.4	0.051
VEGF C-1498T	CC	19		1.3		8	0.301		1	0.395	1.921	0.732		1.67	0.84	3.3	0.141
				15	0.783									8	2	45	
	CC	40	ref	*	*	*	*	ref	*	*	*	*	ref	*	*	*	*
VEGF G-1154A	CT	47		1.5		9	0.063		1.01	0.547	1.892	0.958		1.88	1.02	3.4	0.043
				12	0.978	7			7					8	1	89	
	TT	42		1.2		7	0.3		0.85	0.454	1.6	0.619		1.47	0.78	2.7	0.234
VEGF G-1154A	GG	46	ref	*	*	*	*	ref	*	*	*	*	ref	*	*	*	*
				1.3		3	0.158		1.12	0.602	2.086	0.719		1.69	0.81	3.5	0.156
	AG	31		97	0.878	2			1					7	7	23	
ICAM1 T469C	AA	41		1.0		2	0.97		1.83	0.961	3.487	0.066		0.79	0.44	1.4	0.431
				08	0.659				1					1	1	18	
	TT	46	ref	*	*	*	*	ref	*	*	*	*	ref	*	*	*	*
ICAM1 T469C				1.1		3			0.77								
	CT	57		68	0.788	4	0.439		6	0.452	1.332	0.358		1.60	0.88	2.8	0.117
				0.9		4			0.81					4	8	95	
ICAM1 T469C	AA	26		27	0.572	4	0.76		6	0.391	1.701	0.587		1.10	0.57	2.1	0.771
														2	2	24	

FGFR4 G388A	GG	56	ref	*	*	*	*	*	*	ref	*	*	*	*	*
				0.8			1.22		0.67						
	AG	53		36	0.569	8	0.361		6	0.398	1.15	0.149		0.79	1.4
EGF A+61G	AA	12		0.6			1.23		0.59						
				21	0.313		0.172		8	0.196	1.822	0.366		0.67	1.5
	AA	27	ref	*	*	*	*	*	*	*	*	*	ref	*	*
	AG	62		0.9			1.46		0.79						
				29	0.588	7	0.753		5	0.421	1.504	0.481		1.05	2.0
	GG	39		0.6			0.124		0.39					1.06	2.1
EGFR G497A	GG	21	ref	*	*	*	*	*	*	ref	*	*	*	*	*
				1.4			2.36		1.84					1.34	2.8
	AG	67		29	0.863	5	0.165		3	0.93	3.65	0.08		2	77
IL8 T- 251A	AA	41		1.2			2.08		1.08					1.51	3.3
				13	0.706	2	0.484		2	0.513	2.285	0.836		5	56
	TT	72	ref	*	*	*	*	*	*	ref	*	*	*	*	*
	AT or AA	59		0.9			1.36		1.03					0.75	1.2
				6	0.676	5	0.822		7	0.636	1.69	0.885		1	7

CXCR2	CC	27	ref	*	*	*	*	*	*	*	*	*	ref	*	*	*	*	*
C+785T	CT	56		0.8	4	0.527	1	1.34	0.466		1.08	3		0.60	9	0.29	1.2	*
	TT	48		0.7	92	0.493	4	1.27	0.336		1.45	1		0.47	7	0.23	0.9	0.177
ERCC1	CC	39	ref	*	*	*	*	*	*	*	*	*	ref	*	*	*	*	*
	CT	56		1.0	2	0.672	6	1.54	0.927		0.93	5		0.89	4	0.46	1.7	0.734
	TT	35		1.3	21	0.833	4	2.09	0.237		1.18	9		1.63	1	0.89	2.9	0.11
ERCC1	CC	67	ref	*	*	*	*	*	*	*	*	*	ref	*	*	*	*	*
3'UTR	AC	49		0.6	94	0.477	1.01		0.056		0.56	9		0.73	6	0.42	1.2	0.266
	AA	13		0.6	72	0.37	2	1.22	0.193		0.57	2		0.54	5	0.19	1.5	0.255

XPD A751C	AA	43	ref	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
				1.0			1.61		1.07										
	AC	68		91	0.738	2	0.663		5	0.594	1.946	0.811		0.93	1	0.54	1.5		0.793
XPD C156A	CC	19		1.2	0.07		2.08	7	2.14	2	0.942	4.871	0.069		0.82	1	0.38	1.7	0.614
	CC	56	ref	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	AC	51		0.9	66	0.656	2	1.42	1.09	4	0.645	1.855	0.739		0.79	1	0.44	1.4	0.431
XRCC1 G- 399A	AA	20		0.8	91	0.526	9	1.50	0.72	4	0.326	1.606	0.427		1.13	8	0.56	11	0.721
	GG	52	ref	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	AG	69		0.7	52	0.522	4	1.08	0.69	9	0.424	1.152	0.16		0.81	4	0.47	1.4	0.46
COX2 G- 765C	AA	10		0.7	77	0.393	6	1.53	2.85	1	0.842	9.661	0.093		0.70	5	0.29	1.6	0.432
	GG	60	ref	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	CG	47		0.8	75	0.595	8	1.28	0.60	6	0.351	1.047	0.073		1.14	3	0.64	2.0	0.647
	CC	16		0.9	82	0.561	9	1.71	0.41	7	0.142	1.229	0.113		1.63	2	0.79	3.3	0.184

GSTP1 A105G	AA	66	ref	*	*	*	*	*	*	*	*	ref	*	*	*	*	*	*	*	*			
	AG	51		1.0	46	0.723	1.51	2	0.813		1.70	7	1	2.912	0.05		0.92	8	0.54	1.5	91	0.786	
	GG	13		0.7	34	0.393	1.37	0.332		0.88	0.339	2.287	0.794		0.67	9	0.28	1.5	98	0.376			
KDR EXON 11 T/A	TT	57	ref	*	*	*	*	*	*	*	*	ref	*	*	*	*	*	*	*	*	*		
	TA or AA	75		0.6	85	0.48	0.97	7	0.037		0.48	2	0.284	0.818	0.007		0.86	1	0.51	1.4	32	0.565	
WNK1rs1 1064560 T/G	TT	53	ref	*	*	*	*	*	*	*	*	ref	*	*	*	*	*	*	*	*	*		
	GT	61		0.9	03	0.621	1.31	2	0.593		0.87	5	0.513	1.493	0.625		0.97	8	0.57	1.6	4	67	0.934
	GG	17		1.3	56	0.778	2.36	4	0.283		0.85	5	0.414	1.768	0.674		2.61	5	1.07	6.3	5	57	0.034

[illegible]

Response

[0361] Overall, patients with the mutant homozygote for ICAM1-469 had a significantly higher response rate than the others ($p=0.04$). The other finding was that among patients treated on the PC arm, those with the ERCC1-3'UTR mutant homozygote had a

5 significantly higher response rate when compared to the other two groups ($p=0.039$).

[0362] Response rates, percentages, and p-values are provided in Table 4.

Table 4. Response among those eligible patients with measurable disease

Polymorphism	Genotype	# cr/pr	%	p-value	# cr/pr	%	p-value	# cr/pr	%	p-value
VEGF C+936T	CC	21	0.214		8	0.151		13	0.289	
	CT or TT	5	0.250		0	0.000		5	0.455	
VEGF G-634C	GG	13	0.210		2	0.065		11	0.355	
	GC	7	0.189		5	0.208		2	0.154	
	CC	5	0.278	0.744	1	0.125	0.267	4	0.400	0.347
VEGF C-1498T	CC	8	0.222		1	0.059		7	0.368	
	CT	9	0.205		3	0.125		6	0.300	
	TT	9	0.250	0.960	4	0.190	0.505	5	0.333	0.935
VEGF G-1154A	GG	9	0.237		3	0.150		6	0.333	
	AG	5	0.172		2	0.111		3	0.273	
	AA	7	0.184	0.825	0	0.000	0.353	7	0.350	1.000
ICAM1 T469C	TT	8	0.200		2	0.091		6	0.333	
	CT	7	0.132		3	0.100		4	0.174	
	CC	9	0.391	0.040	3	0.273	0.325	6	0.500	0.125

FGFR4 G388A	GG	9	0.188		2	0.087		7	0.280	
	AG	11	0.224		5	0.161		6	0.333	
	AA	2	0.182	0.939	1	0.200	0.613	1	0.167	0.826
EGF A+61G	AA	4	0.167		1	0.077		3	0.273	
	AG	10	0.179		2	0.065		8	0.320	
	GG	11	0.314	0.277	5	0.278	0.123	6	0.353	1.000
EGFR G497A	GG	4	0.250		3	0.375		1	0.125	
	AG	13	0.206		3	0.081		10	0.385	
	AA	8	0.216	0.950	2	0.111	0.135	6	0.316	0.451
IL8 T- 251A	TT	15	0.238		3	0.103		12	0.353	
	AT or AA	10	0.189		5	0.152		5	0.250	
CXCR2 C+785T	CC	3	0.115		2	0.133		1	0.091	
	CT	10	0.213		2	0.080		8	0.364	
	TT	12	0.267	0.324	4	0.174	0.637	8	0.364	0.265
ERCC1 C118T	CC	8	0.229		2	0.105		6	0.375	
	CT	13	0.255		6	0.176		7	0.412	
	TT	4	0.129	0.393	0	0.000	0.590	4	0.182	0.247
ERCC1 3'UTR C/A	CC	10	0.161		1	0.034		9	0.273	
	AC	10	0.233		4	0.160		6	0.333	
	AA	5	0.417	0.153	3	0.333	0.039	2	0.667	0.384
XPD A751C	AA	6	0.167		2	0.143		4	0.182	
	AC	14	0.222		5	0.128		9	0.375	
	CC	5	0.278	0.639	1	0.100	1.000	4	0.500	0.178
XPD C156A	CC	14	0.280		6	0.222		8	0.348	
	AC	7	0.149		1	0.036		6	0.316	
	AA	4	0.211	0.290	1	0.125	0.116	3	0.273	1.000

XRCC1 G-399A	GG	10	0.213		5	0.172		5	0.278	
	AG	12	0.197		3	0.097		9	0.300	
	AA	3	0.300	0.748	0	0.000	0.647	3	0.429	0.839
COX2 G- 765C	GG	12	0.214		2	0.059		10	0.455	
	CG	10	0.250		5	0.238		5	0.263	
	CC	2	0.143	0.809	0	0.000	0.145	2	0.200	0.341
GSTP1 A105G	AA	12	0.211		5	0.139		7	0.333	
	AG	11	0.224		2	0.091		9	0.333	
	GG	2	0.182	1.000	1	0.200	0.617	1	0.167	0.837
KDR EXON 11 T/A	TT	11	0.204		3	0.100		8	0.333	
	TA or AA	14	0.226		5	0.156		9	0.300	
WNK1rs 1106456 0 T/G	TT	12	0.245		3	0.111		9	0.409	
	GT	12	0.222		4	0.148		8	0.296	
	GG	2	0.133	0.746	1	0.111	1.000	1	0.167	0.554
WNK1rs 2158501 G/A	GG	10	0.244		3	0.150		7	0.333	
	AG	9	0.209		3	0.130		6	0.300	
	AA	4	0.138	0.583	2	0.105	1.000	2	0.200	0.853

Toxicity

[0363] Bevacizumab-induced hypertension has been studied in a few other settings, most recently by the ECOG breast committee on study E2100. They found that haplotypes that contained alleles advantageous for survival never included alleles that protected against hypertension (VEGF634C and VEGF1498T). It was of interest to try to find a connection between these alleles and the incidence of hypertension on the bevacizumab arm. The problem, however, is that there is hardly any power to do this. There were a total of 30 cases on E4599 who reported grade3-4 hypertension of any attribution type on this study. Once

these cases are merged with the correlatives dataset, there is an overlap of only 7 hypertension cases in the correlative study. The distribution of hypertension versus genotype for these VEGF polymorphisms, as well as the WNK1 polymorphisms is as follows:

<u>VEGF634</u>	No HTN	HTN
CC	10	1
GC	15	0
GG	31	6

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<u>VEGF1498</u>	No HTN	HTN
CC	18	4
CT	21	1
TT	17	2

<u>WNK1-110644560</u>	No HTN	HTN
GG	7	0
GT	32	1
TT	18	6

<u>WNK1-2158501</u>	No HTN	HTN
GG	12	1
GT	22	2
TT	18	4

[0364] Interestingly, if we look at WNK1-110644560 and group the GG and GT groups to test against the TT group, there is a statistically significant imbalance in the HTN rate in the groups ($p=0.009$). Note that this group (GG) had 3.198 times the risk of death when compared to the (TT) group ($p=0.012$) when fitted to the BPC arm only. They also had 2.615 times the risk of progression/death when compared to the (TT) group ($p=0.034$). (See Tables 2 and 3 for results).

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Multivariable Models adjusted for gender, PS, stage, adrenal mets, liver mets, and bone mets. All models also adjust for the genotypes and treatment arm.

[0365] OVERALL SURVIVAL

1. VEGF634: The interaction between bev and VEGF634-**GC** (p=0.01).
2. ICAM1-469: Interaction between bev and ICAM1-469-**CC** (p=0.037).
3. ERCC1-118: Comparing **TT** to **CC** (not an interaction), remained significant in a multivariable model (p=0.036) even though not significant on the univariate level.
4. ERCC1-UTR: Not interactions, but each genotype **AC and AA** were significant when compared to **CC** (p=0.002 and 0.06, respectively).
5. GSTP1-105: The interaction between **AG** and bev remained significant (p=0.022).
6. WNK1-11064560: The interaction between **GG** and bev remained significant (p=0.022).
7. Not interactions, but **AG and AA** remained significant when compared to **GG** (p=0.007 and 0.04, respectively)

[0366] PROGRESSION-FREE SURVIVAL

1. ICAM1-469: Interaction between **CT** and bev (p=0.02).
2. EGF-61: Interaction between **GG** and bev (p=0.038)
3. CXCR2-785: Interaction between **TT** and bev (P=0.027)
4. ERCC1-UTR: Not interactions but **AC and AA** remained significant when compared to **AA** (p=0.03 for each)
5. XPD751: Interaction between bev and **CC** (p=0.046).
6. XPD156: Interaction between **AA** and bev (p=0.025).
7. GSTP1-105: **AG** remained significant in a multivariable model (p=0.03).
8. KDR: Interaction of (**TA or AA**) with bev (p=0.057).
9. WNK1-2158501: **AG** remained significant in multivariable model (p=0.02).

RECURSIVE PARTITIONING

[0367] Cox models were fitted by treatment arm adjusting for each of the 20 SNPs in Dr. Lenz's lab data. Each SNP was categorized into two groups: the reference group vs. everything else. In the recursive partitioning trees, at each split a SNP is labeled on the tree and the genotype reference after the SNP name is the reference group.

Brief summary:

[0368] For OS on the Bev arm, it appears that the most important SNP is ICAM, followed by VEGF 634 and VEGF 1498. For PFS on this arm, the most important SNPs are VEGF634, followed by CXCR2785 and KDR.

- 5 **[0369]** For OS on the PC arm, it appears that the most important SNP is VEGF634, followed by IL8251 and FGFR388. For PFS on this arm, the most important SNPs are ERCC13UTR, followed by XRCC1399 and KDR.

[0370] The numbers under each rectangle box in the figures are the medians and 95% confidence intervals for the patients with SNP profiles corresponding to each arm of the recursive partitioning tree. The fractions (in the OS and PFS plots) represent the number of patients with events / number at risk. Since each SNP was coded in the modeling as a dichotomous value (0=reference group/homozygous WT group vs. 1=homozygous or heterozygous mutant group), the way to read each arm of the tree, for example, is:

15 **[0371]** $Icam469_{tt} < 0.5 \rightarrow$ This means patients for whom ICAM469 TT=0 (TT is the reference/homozygous WT group)

[0372] $Icam469_{tt} \geq 0.5 \rightarrow$ This means patients for whom ICAM469 TT=1 (Genotype not equal to TT/Mutant group)

[0373] It is to be understood that while the invention has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

What is claimed is:

1. A method for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving an anti-VEGF-based therapy, comprising determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR
5 exon 11 T>A, GSTP1 A105G, or WNK1 rs11064560 T>G, wherein the presence of at least one genotype of:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- 10 c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (A/G or G/G) for GSTP1 A105G; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a longer overall survival, or the presence of
15 none of genotypes a) to f) identifies the patient as likely to experience a shorter overall survival.

2. The method of claim 1, wherein the presence of at least one genotype of:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- 20 c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (A/G or G/G) for GSTP1 A105G; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

identifies the patient as likely to experience a longer overall survival.

25 3. The method of claim 1 or 2, wherein the patient that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than a patient suffering from the cancer, receiving the therapy and having none of genotypes a) to f).

4. The method of claim 1, wherein the presence of none of genotypes a) to f) identifies
30 the patient as likely to experience a shorter overall survival.

5. The method of claim 1 or 4, wherein the patient that is likely to experience a shorter overall survival is a patient that is likely to experience a relatively shorter overall survival than a patient suffering from the cancer, receiving the therapy and having at least one of genotypes a) to f).

5 6. A method for treating a cancer patient selected as likely to experience a longer overall survival from receiving an anti-VEGF based therapy, based on the presence of at least one genotype of the group:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- 10 c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (A/G or G/G) for GSTP1 A105G; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

15 in a sample from the patient, comprising administering the therapy to the cancer patient, thereby treating the patient.

7. Use of an anti-VEGF based therapy for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (T/T or C/C) for ICAM1 T469C;
- 20 b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (A/G or G/G) for GSTP1 A105G; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

25 in a sample from the patient.

8. An anti-VEGF based therapy for use in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (T/T or C/C) for ICAM1 T469C;
- 30 b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;

- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (A/G or G/G) for GSTP1 A105G; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

in a sample from the patient.

- 5 9. The method of claim 6, the use of claim 7, or the therapy of claim 8, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, GSTP1 A105G, or WNK1 rs11064560 T>G.

- 10 10. A method for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving an anti-VEGF-based therapy, comprising determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A, wherein the presence of at least one genotype of:

- a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
- 15 b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or
- c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A or A/T) for IL-8 T-251A,

- identifies the patient as likely to experience a longer overall survival, or the presence of none of genotypes a) to c) identifies the patient as likely to experience a shorter overall survival.
- 20

11. The method of claim 10, wherein the presence of at least one genotype of:

- a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
 - b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or
 - c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A or A/T) for IL-8 T-251A,
- 25

identifies the patient as likely to experience a longer overall survival.

12. The method of claim 10 or 11, wherein the patient that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than a patient suffering from the cancer, receiving the therapy and having none of genotypes a) to c).
- 30

13. The method of claim 10, wherein the presence of none of genotypes a) to c) identifies the patient as likely to experience a shorter overall survival.

14. The method of claim 10 or 13, wherein the patient that is likely to experience a shorter overall survival is a patient that is likely to experience a relatively shorter overall survival than a patient suffering from the cancer, receiving the therapy and having at least one of genotypes a) to c).

15. A method for treating a cancer patient selected as likely to experience a longer overall survival from receiving an anti-VEGF based therapy, based on the presence of at least one genotype of the group:

- 10 a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
 b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or
 c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A or A/T) for IL-8 T-251A,
in a sample from the patient, comprising administering the therapy to the cancer patient,
15 thereby treating the patient.

16. Use of an anti-VEGF based therapy for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
20 b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or
 c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A or A/T) for IL-8 T-251A,
in a sample from the patient.

17. An anti-VEGF based therapy for use in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (T/T) for ICAM1 T469C and (G/G) for VEGF G-634C;
 b) (T/T) for ICAM1 T469C and (A/G or A/A) for VEGF G-634C; or
 c) (A/A or A/T) for ICAM1 T469C, (T/T or C/T) for VEGF C-1498T and (A/A

or A/T) for IL-8 T-251A,
in a sample from the patient.

18. The method of claim 15, the use of claim 16, or the therapy of claim 17, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the
5 patient for at least two polymorphisms of the group ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A.

19. A method for predicting overall survival of a cancer patient receiving an anti-VEGF-based therapy, comprising:

- a) determining genotypes for at least two polymorphisms of the group ICAM1
10 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A in a cell or tissue sample isolated from the patient; and
- b) combining the genotypes using a suitable mathematical algorithm to predict the length of overall survival of the patient.

20. The method of claim 19, wherein the at least two polymorphisms comprise at least
15 three polymorphisms of the group.

21. The method of claim 19 or 20, wherein the at least two polymorphisms comprise ICAM1 T469C.

22. The method of any one of claims 19 to 21, wherein the at least two polymorphisms comprise ICAM1 T469C and VEGF G-634C.

20 23. The method of any one of claims 19 to 22, wherein the suitable mathematical algorithm of step b) is selected from the group: recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal component analysis.

24. The method of any one of claims 19 to 23, wherein the suitable mathematical
25 algorithm of step b) is recursive partitioning.

25. A method for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving an anti-VEGF-based therapy, comprising determining a genotype of a cell or tissue sample isolated from the patient for at

least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF G-634C, VEGF C-1498T, CXCR2 C+785T, or WNK1 rs11064560 T>G, wherein a genotype of:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- 5 b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- d) (C/C or T/T) for VEGF C-1498T;
- e) (T/T or C/T) for CXCR2 C+785T; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

10 identifies the patient as likely to experience a longer progression survival, or the presence of none of genotypes a) to f) identifies the patient as likely to experience a shorter progression free survival.

26. The method of claim 25, wherein the presence of at least one genotype of:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- 15 b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- d) (C/C or T/T) for VEGF C-1498T;
- e) (T/T or C/T) for CXCR2 C+785T; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

20 identifies the patient as likely to experience a longer progression free survival.

27. The method of claim 25 or 26, wherein the patient that is likely to experience a longer progression free survival is a patient that is likely to experience a relatively longer progression free survival than a patient suffering from the cancer, receiving the therapy and having none of genotypes a) to f).

25 28. The method of claim 25, wherein the presence of none of genotypes a) to f) identifies the patient as likely to experience a shorter progression free survival.

29. The method of claim 25 or 28, wherein the patient that is likely to experience a shorter progression free survival is a patient that is likely to experience a relatively shorter progression free survival than a patient suffering from the cancer, receiving the therapy and
30 having at least one of genotypes a) to f).

30. A method for treating a cancer patient selected as likely to experience a longer progression free survival from receiving an anti-VEGF based therapy, based on the presence of at least one genotype of the group:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- 5 b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- d) (C/C or T/T) for VEGF C-1498T;
- e) (T/T or C/T) for CXCR2 C+785T; or
- f) (T/T or G/T) for WNK1 rs11064560 T>G,

10 in a sample from the patient, comprising administering the therapy to the cancer patient, thereby treating the patient.

31. Use of an anti-VEGF based therapy for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- 15 a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- d) (C/C or T/T) for VEGF C-1498T;
- e) (T/T or C/T) for CXCR2 C+785T; or
- 20 f) (T/T or G/T) for WNK1 rs11064560 T>G,

in a sample from the patient.

32. An anti-VEGF based therapy for use in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- 25 a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or C/C) for VEGF G-634C;
- d) (C/C or T/T) for VEGF C-1498T;
- e) (T/T or C/T) for CXCR2 C+785T; or
- 30 f) (T/T or G/T) for WNK1 rs11064560 T>G,

in a sample from the patient.

33. The method of claim 30, the use of claim 31, or the therapy of claim 32, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF G-634C, VEGF C-1498T, CXCR2 C+785T, or WNK1 rs11064560 T>G.

5 34. A method for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving an anti-VEGF-based therapy, comprising determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C, wherein the presence of at least one genotype of:

10 a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or A/A) for ERCC1 3'UTR C>A; or

b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C,

identifies the patient as likely to experience a longer progression free survival, or the

15 presence of neither genotype a) nor b) identifies the patient as likely to experience a shorter progression free survival.

35. The method of claim 34, wherein the presence of at least one genotype of:

a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or A/A) for ERCC1 3'UTR C>A; or

20 b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C,

identifies the patient as likely to experience a longer progression free survival.

36. The method of claim 34 or 35, wherein the patient that is likely to experience a

longer progression free survival is a patient that is likely to experience a relatively longer

25 progression free survival than a patient suffering from the cancer, receiving the therapy and having neither genotype a) nor b).

37. The method of claim 34, wherein the presence of neither genotype a) nor b)

identifies the patient as likely to experience a shorter progression free survival.

38. The method of claim 34 or 37, wherein the patient that is likely to experience a shorter progression free survival is a patient that is likely to experience a relatively shorter progression free survival than a patient suffering from the cancer, receiving the therapy and having at least one of genotypes a) or b).

5 39. A method for treating a cancer patient selected as likely to experience a longer progression free survival from receiving an anti-VEGF based therapy, based on the presence of at least one genotype of the group:

a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or A/A) for ERCC1 3'UTR C>A; or

10 b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C,
in a sample from the patient, comprising administering the therapy to the cancer patient, thereby treating the patient.

40. Use of an anti-VEGF based therapy for the manufacture of a medicament in treating
15 a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or A/A) for ERCC1 3'UTR C>A; or

20 b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C,
in a sample from the patient.

41. An anti-VEGF based therapy for use in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

25 a) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, and (C/A or A/A) for ERCC1 3'UTR C>A; or

b) (G/G) for VEGF G-634C, (C/T or T/T) for CXCR2 C+785T, (C/C) for ERCC1 3'UTR C>A, and (G/G) for COX-2 G-765C,
in a sample from the patient.

42. The method of claim 39, the use of claim 40, or the therapy of claim 41, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C.

5 43. A method for predicting progression free survival of a cancer patient receiving an anti-VEGF-based therapy, comprising:

a) determining genotypes for at least two polymorphisms of the group VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C in a cell or tissue sample isolated from the patient; and

10 b) combining the genotypes using a suitable mathematical algorithm to predict the length of progression free survival of the patient.

44. The method of claim 43, wherein the at least two polymorphisms comprise at least three polymorphisms of the group.

15 45. The method of claim 43 or 44, wherein the at least two polymorphisms comprises VEGF G-634C.

46. The method of any one of claims 43 to 45, wherein the at least two polymorphisms comprise VEGF G-634C and CXCR2 C+785T.

20 47. The method of any one of claims 43 to 46, wherein the suitable mathematical algorithm of step b) is selected from the group: recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal component analysis.

48. The method of any one of claims 43 to 47, wherein the suitable mathematical algorithm of step b) is recursive partitioning.

25 49. A method for identifying a patient having a cancer more or less likely to respond to an anti-VEGF-based therapy, comprising determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, COX2 G-765C or WNK1 rs11064560 T>G, wherein the presence of at least one genotype of:

a) (C/C) for ICAM1 T469C; or

b) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G, identifies the patient as more likely to respond to the therapy, or the presence of neither a) nor b) identifies the patient as less likely to respond to the therapy.

50. The method of claim 49, wherein the presence of at least one genotype of:

- 5 a) (C/C) for ICAM1 T469C; or
b) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G,
identifies the patient as more likely to respond to the therapy.

51. The method of claim 49 or 50, wherein the patient that is more likely to respond to the therapy is a patient that is relatively more likely to respond to the therapy than a patient
10 suffering from the cancer, receiving the therapy and having neither genotype a) nor b).

52. The method of claim 49, wherein the presence of neither a) nor b) identifies the patient as less likely to respond to the therapy.

53. The method of claim 49 or 52, wherein the patient that is less likely to respond to the therapy is a patient that is relatively less likely to respond to the therapy than a patient
15 suffering from the cancer, receiving the therapy and having at least one genotype of a) or b).

54. A method for treating a cancer patient selected as more likely to respond to an anti-VEGF based therapy, based on the presence of at least one genotype of:

- a) (C/C) for ICAM1 T469C; or
b) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G,
20 in a sample from the patient, comprising administering the therapy to the cancer patient, thereby treating the patient.

55. Use of an anti-VEGF based therapy for the manufacture of a medicament in treating a cancer patient selected as more likely to respond to an anti-VEGF based therapy, based on the presence of at least one genotype of:

- 25 a) (C/C) for ICAM1 T469C; or
b) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G,
in a sample from the patient.

56. An anti-VEGF based therapy for use in treating a cancer patient selected as more likely to respond to an anti-VEGF based therapy, based on the presence of at least one genotype of:

- a) (C/C) for ICAM1 T469C; or
 - 5 b) (G/G) for COX2 G-765C and (T/T) for WNK1 rs11064560 T>G,
- in a sample from the patient.

57. The method of claim 54, the use of claim 55, or the therapy of claim 56, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, COX2 G-765C or
10 WNK1 rs11064560 T>G.

58. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, or 57, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55 or 57, or the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56 or 57, wherein the anti-VEGF-based therapy comprises administration of an anti-VEGF antibody, a VEGF inhibitor, or an equivalent
15 thereof.

59. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, 57 or 58, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55, 57 or 58, or the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56, 57 or 58, wherein the anti-VEGF-based therapy comprises administration of bevacizumab or an equivalent thereof.

20 60. The method of claim 58 or 59, wherein the anti-VEGF-based therapy further comprises administration of a platinum drug.

61. The method of claim 60, wherein the platinum drug is carboplatin or an equivalent thereof.

62. The method of any one of claims 58 to 61, wherein the anti-VEGF-based therapy
25 further comprises administration of a mitotic inhibitor.

63. The method of claim 62, wherein the mitotic inhibitor is paclitaxel or an equivalent thereof.

64. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, or 57 to 63, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55 or 57 to 63, or the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56 or 57 to 63, wherein the anti-VEGF-based therapy comprises administration of an anti-VEGF antibody in combination with a platinum drug and a mitotic inhibitor.

65. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, or 57 to 64, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55 or 57 to 64, or the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56 or 57 to 64, wherein the anti-VEGF-based therapy comprises administration of bevacizumab or an equivalent thereof in combination with carboplatin or an equivalent thereof, and paclitaxel or an equivalent thereof.

66. The method of claim 64 or 65, wherein the administration of the anti-VEGF antibody, the platinum drug or the mitotic inhibitor is concurrent or sequential.

67. A method for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF C-1498T, VEGF G-1154A, EGF A+61G, or COX2 G-765C, wherein the presence of at least one genotype of:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (T/T or C/T) for VEGF C-1498T;
- f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

identifies the patient as likely to experience a longer overall survival, or the presence of none of the genotypes a) to g) identifies the patient as likely to experience a shorter overall survival.

68. The method of claim 67, wherein the presence of at least one genotype of:

- a) (T/T or C/C) for ICAM1 T469C;

- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (T/T or C/T) for VEGF C-1498T;
- 5 f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

identifies the patient as likely to experience a longer overall survival.

69. The method of claim 67 or 68, wherein the patient that is likely to experience a longer overall survival is a patient that is likely to experience a relatively longer overall survival than a patient suffering from the cancer, receiving the therapy and having none of genotypes a) to g).

70. The method of claim 67, wherein the presence of none of genotypes a) to g) identifies the patient as likely to experience a shorter overall survival.

71. The method of claim 67 or 70, wherein the patient that is likely to experience a shorter overall survival is a patient that is likely to experience a relatively shorter overall survival than a patient suffering from the cancer, receiving the therapy and having at least one of genotypes a) to g).

72. A method for treating a cancer patient selected as likely to experience a longer overall survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, based on the presence of at least one genotype of the group:

- a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- 25 e) (T/T or C/T) for VEGF C-1498T;
- f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

in a sample from the patient, comprising administering the therapy to the cancer patient, thereby treating the patient.

73. Use of a therapy comprising a platinum drug and a mitotic inhibitor for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- 5 a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- e) (T/T or C/T) for VEGF C-1498T;
- 10 f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

in a sample from the patient.

74. A therapy comprising a platinum drug and a mitotic inhibitor for use in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- 15 a) (T/T or C/C) for ICAM1 T469C;
- b) (C/T or T/T) for CXCR2 C+785T;
- c) (A/C or A/A) for ERCC1 3'UTR C>A;
- d) (A/T or A/A) for KDR exon 11 T>A;
- 20 e) (T/T or C/T) for VEGF C-1498T;
- f) (G/G or A/G) for VEGF G-1154A; or
- g) (C/C or C/G) for COX2 G-765C,

in a sample from the patient.

75. The method of claim 72, the use of claim 73, or the therapy of claim 74, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF C-1498T, VEGF G-1154A, EGF A+61G, or COX2 G-765C.

76. A method for identifying a patient having a cancer that is likely to experience a longer or shorter overall survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising determining a genotype of a cell or tissue sample isolated from

the patient for at least two polymorphisms of the group VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A, wherein the presence of at least one genotype of:

- a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;
- 5 b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G) for VEGF G-1154A; or
- c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or A/A) for VEGF G-1154A,

identifies the patient as likely to experience a longer overall survival, or the presence of
10 none of genotypes a) to c) identifies the patient as likely to experience a shorter overall survival.

77. The method of claim 76, wherein the presence of at least one genotype of:

- a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;
- b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G)
- 15 for VEGF G-1154A; or
- c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or A/A) for VEGF G-1154A,

identifies the patient as likely to experience a longer overall survival.

78. The method of claim 76 or 77, wherein the patient that is likely to experience a
20 longer overall survival is a patient that is likely to experience a relatively longer overall survival than a patient suffering from the cancer, receiving the therapy and having none of genotypes a) to c).

79. The method of claim 77, wherein the presence of none of genotypes a) to c) identifies the patient as likely to experience a shorter overall survival.

25 80. The method of claim 77 or 79, wherein the patient that is likely to experience a shorter overall survival is a patient that is likely to experience a relatively shorter overall survival than a patient suffering from the cancer, receiving the therapy and having at least one of genotypes a) to c).

81. A method for treating a cancer patient selected as likely to experience a longer overall survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, based on the presence of at least one genotype of the group:

- a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;
 - 5 b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G) for VEGF G-1154A; or
 - c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or A/A) for VEGF G-1154A,
- in a sample from the patient, comprising administering the therapy to the cancer patient,
- 10 thereby treating the patient.

82. Use of a therapy comprising a platinum drug and a mitotic inhibitor for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- 15 a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;
 - b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G) for VEGF G-1154A; or
 - c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or A/A) for VEGF G-1154A,
- 20 in a sample from the patient.

83. A therapy comprising a platinum drug and a mitotic inhibitor for use in treating a cancer patient selected as likely to experience a longer overall survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (G/C or C/C) for VEGF G-634C and (T/T) for IL-8 T-251A;
 - 25 b) (G/C or C/C) for VEGF G-634C, (A/T or A/A) for IL-8 T-251A, and (G/G) for VEGF G-1154A; or
 - c) (G/G) for VEGF G-634C, (A/G or A/A) for FGFR4 G388A, and (T/A or A/A) for VEGF G-1154A,
- in a sample from the patient.

- 30 84. The method of claim 81, the use of claim 82, or the therapy of claim 83, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the

patient for at least two polymorphisms of the group VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A.

85. A method for predicting overall survival of a cancer patient receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising:

- 5 a) determining genotypes for at least two polymorphisms of the group VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A in a cell or tissue sample isolated from the patient; and
- b) combining the genotypes using a suitable mathematical algorithm to predict the length of overall survival of the patient.

10 86. The method of claim 85, wherein the at least two polymorphisms comprise at least three polymorphisms of the group.

87. The method of claim 85 or 86, wherein the at least two polymorphisms comprise VEGF G-634C.

15 88. The method of any one of claims 85 to 87, wherein the at least two polymorphisms comprise VEGF G-634C and IL-8 T-251A.

89. The method of any one of claims 85 to 88, wherein the suitable mathematical algorithm of step b) is selected from the group: recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal component analysis.

20 90. The method of any one of claims 85 to 89, wherein the suitable mathematical algorithm of step b) is recursive partitioning.

91. A method for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising determining a genotype of a cell or tissue sample

25 isolated from the patient for at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, EGF A+61G, and GSTP1 A105G, wherein the presence of at least one genotype of:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;

- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or A/G) for EGF A+61G; or
- d) (A/A or G/G) for GSTP1 A105G,

identifies the patient as likely to experience a longer progression free survival, or the
5 presence of none of a) to d) identifies the patient as likely to experience a shorter
progression free survival.

92. The method of claim 91, wherein the presence of at least one genotype of:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- 10 c) (G/G or A/G) for EGF A+61G; or
- d) (A/A or G/G) for GSTP1 A105G,

identifies the patient as likely to experience a longer progression free survival.

93. The method of claim 91 or 92, wherein the patient that is likely to experience a
longer progression free survival is a patient that is likely to experience a relatively longer
15 progression free survival than a patient suffering from the cancer, receiving the therapy and
having none of genotypes a) to d).

94. The method of claim 91, wherein the presence of none of genotypes a) to d)
identifies the patient as likely to experience a shorter progression free survival.

95. The method of claim 91 or 94, wherein the patient that is likely to experience a
20 shorter progression free survival is a patient that is likely to experience a relatively shorter
progression free survival than a patient suffering from the cancer, receiving the therapy and
having at least one of genotypes a) to d).

96. A method for treating a cancer patient selected as likely to experience a longer
progression free survival from receiving a therapy comprising a platinum drug and a mitotic
25 inhibitor, based on the presence of at least one genotype of the group:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or A/G) for EGF A+61G; or
- d) (A/A or G/G) for GSTP1 A105G,

in a sample from the patient, comprising administering the therapy to the cancer patient, thereby treating the patient.

97. Use of a therapy comprising a platinum drug and a mitotic inhibitor for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or A/G) for EGF A+61G; or
- d) (A/A or G/G) for GSTP1 A105G,

in a sample from the patient.

98. A therapy comprising a platinum drug and a mitotic inhibitor for use in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (A/C or A/A) for ERCC1 3'UTR C>A;
- b) (A/T or A/A) for KDR exon 11 T>A;
- c) (G/G or A/G) for EGF A+61G; or
- d) (A/A or G/G) for GSTP1 A105G,

in a sample from the patient.

99. The method of claim 96, the use of claim 97, or the therapy of claim 98, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the patient for at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, EGF A+61G, and GSTP1 A105G.

100. A method for identifying a patient having a cancer that is likely to experience a longer or shorter progression free survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A, wherein a genotype of:

- a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11 T>A;

b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,
identifies the patient as likely to experience a longer progression free survival, or a genotype
not in the group a) or b) identifies the patient as likely to experience a shorter progression
5 free survival.

101. The method of claim 100, wherein the presence of at least one genotype of:

a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11
T>A;
b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
10 c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,
identifies the patient as likely to experience a longer progression free survival.

102. The method of claim 100 or 101, wherein the patient that is likely to experience a
longer progression free survival is a patient that is likely to experience a relatively longer
progression free survival than a patient suffering from the cancer, receiving the therapy and
15 having none of genotypes a) to c).

103. The method of claim 100, wherein the presence of none of genotypes a) to c)
identifies the patient as likely to experience a shorter progression free survival.

104. The method of claim 100 or 103, wherein the patient that is likely to experience a
shorter progression free survival is a patient that is likely to experience a relatively shorter
20 progression free survival than a patient suffering from the cancer, receiving the therapy and
having at least one of genotypes a) to c).

105. A method for treating a cancer patient selected as likely to experience a longer
progression free survival from receiving a therapy comprising a platinum drug and a mitotic
inhibitor, based on the presence of at least one genotype of the group:

25 a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11
T>A;
b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,

in a sample from the patient, comprising administering the therapy to the cancer patient, thereby treating the patient.

106. Use of a therapy comprising a platinum drug and a mitotic inhibitor for the manufacture of a medicament in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11 T>A;
 - b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
 - c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,
- in a sample from the patient.

107. A therapy comprising a platinum drug and a mitotic inhibitor for use in treating a cancer patient selected as likely to experience a longer progression free survival from receiving the therapy, based on the presence of at least one genotype of the group:

- a) (C/A or A/A) for ERCC1 3'UTR C>A and (T/A or A/A) for KDR exon 11 T>A;
 - b) (C/A or A/A) for ERCC1 3'UTR C>A and (T/T) for KDR exon 11 T>A; or
 - c) (C/C) for ERCC1 3'UTR C>A and (A/G or A/A) for XRCC G-399A,
- in a sample from the patient.

108. The method of claim 105, the use of claim 106, or the therapy of claim 107, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the patient for at least two polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A.

109. A method for predicting progression free survival of a cancer patient receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising:

- a) determining genotypes for at least two polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A in a cell or tissue sample isolated from the patient; and
- b) combining the genotypes using a suitable mathematical algorithm to predict the length of progression free survival of the patient.

110. The method of claim 109, wherein the at least two polymorphisms comprise at least three polymorphisms of the group.

111. The method of claim 109 or 110, wherein the at least two polymorphisms comprise ERCC1 3'UTR C>A.

5 112. The method of any one of claims 109 to 111, wherein the at least two polymorphisms comprise ERCC1 3'UTR C>A and KDR exon 11 T>A.

113. The method of any one of claims 109 to 112, wherein the suitable mathematical algorithm of step b) is selected from the group: recursive partitioning, decision tree, logistic regression, regression analysis, discriminant analysis, artificial neural network, or principal
10 component analysis.

114. The method of any one of claims 109 to 113, wherein the suitable mathematical algorithm of step b) is recursive partitioning.

115. The method of any one of claims 67 to 72, 75 to 81, 84 to 96, 99 to 105, 108 to 114, the use of any one of claims 73, 75, 82, 84, 97, 99, 106 or 108, or the therapy of any one of
15 claims 74, 75, 83, 84, 98, 99, 107 or 108, wherein the platinum drug and mitotic inhibitor combination therapy comprises administration of a platinum drug and a mitotic inhibitor.

116. The method of claim 115, wherein the platinum drug is carboplatin or an equivalent thereof.

117. The method of claim 114 or 115, wherein the mitotic inhibitor is paclitaxel or an
20 equivalent thereof.

118. The method of any one of claims 114 to 117, wherein the administration of the platinum drug and mitotic inhibitor is concurrent or sequential.

119. A method of identifying a patient having a cancer more or less likely to experience a side effect from a chemotherapy, comprising determining a genotype of a cell or tissue
25 sample isolated from the patient for a WNK1 rs110644560 G>T polymorphism, wherein a genotype of (T/T) for WNK1 rs110644560 G>T identifies the patient as more likely to

experience the side effect, or a genotype of (G/G or G/T) for WNK1 rs110644560 G>T identifies the patient as less likely to experience the side effect.

120. The method of claim 119, wherein a genotype of (T/T) for WNK1 rs110644560 G>T identifies the patient as more likely to experience the side effect.

5 121. The method of claim 119 or 120, wherein the patient that is more likely to experience a side effect is a patient that is relatively more likely to experience a side effect than a patient suffering from the cancer, receiving the therapy and having a genotype of (G/G or G/T) for WNK1 rs110644560 G>T.

10 122. The method of claim 119, wherein a genotype of (G/G or G/T) for WNK1 rs110644560 G>T identifies the patient as less likely to experience the side effect.

123. The method of claim 119 or 122, wherein the patient that is less likely to experience a side effect is a patient that is relatively less likely to experience a side effect than a patient suffering from the cancer, receiving the therapy and having a genotype of (T/T) for WNK1 rs110644560 G>T.

15 124. A method for treating a cancer patient selected as less likely to experience a side effect from receiving a, based on the presence of a genotype of (G/G or G/T) for WNK1 rs110644560 G>T in a sample from the patient, comprising administering the therapy to the cancer patient, thereby treating the patient.

20 125. Use of a chemotherapy for the manufacture of a medicament in treating a cancer patient selected as less likely to experience a side effect from receiving a, based on the presence of a genotype of (G/G or G/T) for WNK1 rs110644560 G>T in a sample from the patient.

25 126. A chemotherapy for use in treating a cancer patient selected as less likely to experience a side effect from receiving a, based on the presence of a genotype of (G/G or G/T) for WNK1 rs110644560 G>T in a sample from the patient.

127. The method of claim 124, the use of claim 125, or the therapy of claim 126, wherein the patient was selected by determining a genotype of a cell or tissue sample isolated from the patient for a WNK1 rs110644560 G>T polymorphism.

128. The method of any one of claims 119 to 124 or 127, the use of claim 125 or 127, or the therapy of claim 126 or 127, wherein the side effect is hypertension.

129. The method of any one of claims 119 to 124 or 128, the use of any one of claims 125, 127 or 128, or the therapy of any one of claims 126 to 128, wherein the chemotherapy
5 is an anti-VEGF-based therapy or a therapy comprising a platinum drug and a mitotic inhibitor.

130. The method of any one of claims 119 to 124 or 129, the use of any one of claims 125, or 127 to 129, or the therapy of any one of claims 126 to 129, wherein the chemotherapy comprises administration of carboplatin or an equivalent thereof in
10 combination with paclitaxel or an equivalent thereof.

131. The method of any one of claims 119 to 124 or 130, the use of any one of claims 125, or 127 to 130, or the therapy of any one of claims 126 to 130, wherein the chemotherapy comprises administration of bevacizumab or an equivalent thereof in combination with carboplatin or an equivalent thereof and paclitaxel or an equivalent
15 thereof.

132. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, 57 to 71, 75 to 81, 84 to 96, 99 to 105, 108 to 124, or 127 to 131, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55, 57 to 66, 73, 75, 82, 84, 97, 99, 106, 108, 125 or 127 to 131, or the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56, 57 to 66, 74, 75, 83, 84, 98,
20 99, 107, 108, 126 or 127 to 131, wherein the cancer patient is suffering from at least one cancer of the type of the group: metastatic or non-metastatic rectal cancer, metastatic or non-metastatic colon cancer, metastatic or non-metastatic colorectal cancer, non-small cell lung cancer (NSCLC), metastatic breast cancer, non-metastatic breast cancer, renal cell carcinoma, glioblastoma multiforme, ovarian cancer, hormone-refractory prostate cancer,
25 non-metastatic unresectable liver cancer, head and neck cancer, advanced Kaposi's sarcoma, or metastatic or unresectable locally advanced pancreatic cancer.

133. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, 57 to 71, 75 to 81, 84 to 96, 99 to 105, 108 to 124, or 127 to 132, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55, 57 to 66, 73, 75, 82, 84, 97, 99, 106, 108, 125 or 127 to 132, or

the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56, 57 to 66, 74, 75, 83, 84, 98, 99, 107, 108, 126 or 127 to 132, wherein the cancer patient is suffering from lung cancer.

134. The method of claim 133, wherein the lung cancer is non-small cell lung cancer.

135. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, 57 to 71, 75 to 81, 84 to 96, 99 to 105, 108 to 124, or 127 to 134, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55, 57 to 66, 73, 75, 82, 84, 97, 99, 106, 108, 125 or 127 to 134, or the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56, 57 to 66, 74, 75, 83, 84, 98, 99, 107, 108, 126 or 127 to 134, wherein the sample comprises at least one of a tumor cell, a normal cell adjacent to a tumor, a normal cell corresponding to the tumor tissue type, a blood cell, a peripheral blood lymphocyte, or combinations thereof.

136. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, 57 to 71, 75 to 81, 84 to 96, 99 to 105, 108 to 124, or 127 to 135, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55, 57 to 66, 73, 75, 82, 84, 97, 99, 106, 108, 125 or 127 to 135, or the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56, 57 to 66, 74, 75, 83, 84, 98, 99, 107, 108, 126 or 127 to 135, wherein the sample is at least one of a fixed tissue, a frozen tissue, a biopsy tissue, a resection tissue, a microdissected tissue, or combinations thereof.

137. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, 57 to 71, 75 to 81, 84 to 96, 99 to 105, 108 to 124, or 127 to 136, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55, 57 to 66, 73, 75, 82, 84, 97, 99, 106, 108, 125 or 127 to 136, or the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56, 57 to 66, 74, 75, 83, 84, 98, 99, 107, 108, 126 or 127 to 136, wherein the genotype is determined by a method comprising PCR, PCR-RFLP, sequencing, or microarray.

138. The method of any one of claims 1 to 6, 9 to 15, 18 to 30, 33 to 39, 42 to 54, 57 to 71, 75 to 81, 84 to 96, 99 to 105, 108 to 124, or 127 to 137, the use of any one of claims 7, 9, 16, 18, 31, 33, 40, 42, 55, 57 to 66, 73, 75, 82, 84, 97, 99, 106, 108, 125 or 127 to 137, or the therapy of any one of claims 8, 9, 17, 18, 32, 33, 41, 42, 56, 57 to 66, 74, 75, 83, 84, 98, 99, 107, 108, 126 or 127 to 137, wherein the patient is a human patient.

139. A kit for use in identifying a cancer patient that is likely to experience a longer or shorter overall survival from receiving an anti-VEGF-based therapy, comprising one or

more of a suitable primers or probes or a microarray for screening at least two polymorphisms of the group ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A, and instructions for use therein.

140. A kit for use in identifying a cancer patient that is likely to experience a longer or
5 shorter overall survival from receiving an anti-VEGF-based therapy, comprising one or more of a suitable primers or probes or a microarray for screening at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, GSTP1 A105G, or WNK1 rs11064560 T>G, and instructions for use therein.

141. A kit for use in identifying a cancer patient that is likely to experience a longer or
10 shorter progression free survival from receiving an anti-VEGF-based therapy, comprising comprising one or more of a suitable primers or probes or a microarray for screening at least two polymorphisms of the group VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C, and instructions for use therein.

142. A kit for use in identifying a cancer patient that is likely to experience a longer or
15 shorter progression free survival from receiving an anti-VEGF-based therapy, comprising comprising one or more of a suitable primers or probes or a microarray for screening at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF G-634C, VEGF C-1498T, CXCR2 C+785T, or WNK1 rs11064560 T>G, and instructions for use therein.

20 143. A kit for use in identifying a cancer patient that is more or less likely to respond to an anti-VEGF-based therapy, comprising comprising one or more of a suitable primers or probes or a microarray and instructions for determining a genotype of a cell or tissue sample isolated from the patient for two polymorphisms of the group COX2 G-765C or WNK1 rs11064560 T>G.

25 144. A kit for use in identifying a cancer patient that is likely to experience a longer or shorter overall survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising comprising one or more of a suitable primers or probes or a microarray for screening at least two polymorphisms of the group VEGF G-634C, IL-8 T-

251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A, and instructions for use therein.

145. A kit for use in identifying a cancer patient that is likely to experience a longer or shorter overall survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising comprising one or more of a suitable primers or probes or a
5 microarray for screening at least one polymorphism of the group ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF C-1498T, VEGF G-1154A, EGF A+61G, or COX2 G-765C, and instructions for use therein.

146. A kit for use in identifying a cancer patient that is likely to experience a longer or
10 shorter progression free survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising comprising one or more of a suitable primers or probes or a microarray for screening at least two polymorphisms of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A, and instructions for use therein.

147. A kit for use in identifying a cancer patient that is likely to experience a longer or
15 shorter progression free survival from receiving a therapy comprising a platinum drug and a mitotic inhibitor, comprising comprising one or more of a suitable primers or probes or a microarray for screening at least one polymorphism of the group ERCC1 3'UTR C>A, KDR exon 11 T>A, EGF A+61G, and GSTP1 A105G, and instructions for use therein.

148. A prognostic panel of genetic markers comprising a primer or nucleic acid probe or
20 microarray that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ICAM1 T469C, VEGF G-634C, VEGF C-1498T, or IL-8 T-251A.

149. A prognostic panel of genetic markers comprising a primer or nucleic acid probe or
microarray that identifies a genotype of a patient for at least one or more genetic
25 polymorphism of the group: ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, GSTP1 A105G, or WNK1 rs11064560 T>G.

150. A prognostic panel of genetic markers comprising a primer or nucleic acid probe or microarray that identifies a genotype of a patient for at least one or more genetic

polymorphism of the group: VEGF G-634C, KDR exon 11 T>A, CXCR2 C+785T, ERCC1 3'UTR C>A, or COX G-765C.

151. A prognostic panel of genetic markers comprising a primer or nucleic acid probe or microarray that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF G-634C, VEGF C-1498T, CXCR2 C+785T, or WNK1 rs11064560 T>G.

152. A prognostic panel of genetic markers comprising a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: COX2 G-765C or WNK1 rs11064560 T>G.

153. A prognostic panel of genetic markers comprising a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: VEGF G-634C, IL-8 T-251A, FGFR4 G388A, VEGF G-1154A, or KDR exon 11 T>A.

154. A prognostic panel of genetic markers comprising a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ICAM1 T469C, CXCR2 C+785T, ERCC1 3'UTR C>A, KDR exon 11 T>A, VEGF C-1498T, VEGF G-1154A, EGF A+61G, or COX2 G-765C.

155. A prognostic panel of genetic markers comprising a primer or nucleic acid probe that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ERCC1 3'UTR C>A, KDR exon 11 T>A, or XRCC1 G-399A.

156. A prognostic panel of genetic markers comprising a primer or nucleic acid probe or a microarray that identifies a genotype of a patient for at least one or more genetic polymorphism of the group: ERCC1 3'UTR C>A, KDR exon 11 T>A, EGF A+61G, and GSTP1 A105G.

157. The panel of any one of claims 148 to 156, wherein the primer or probe is attached to a microarray.

158. The panel of any one of claims 148 to 157, wherein the primer or probe is detectably labeled.

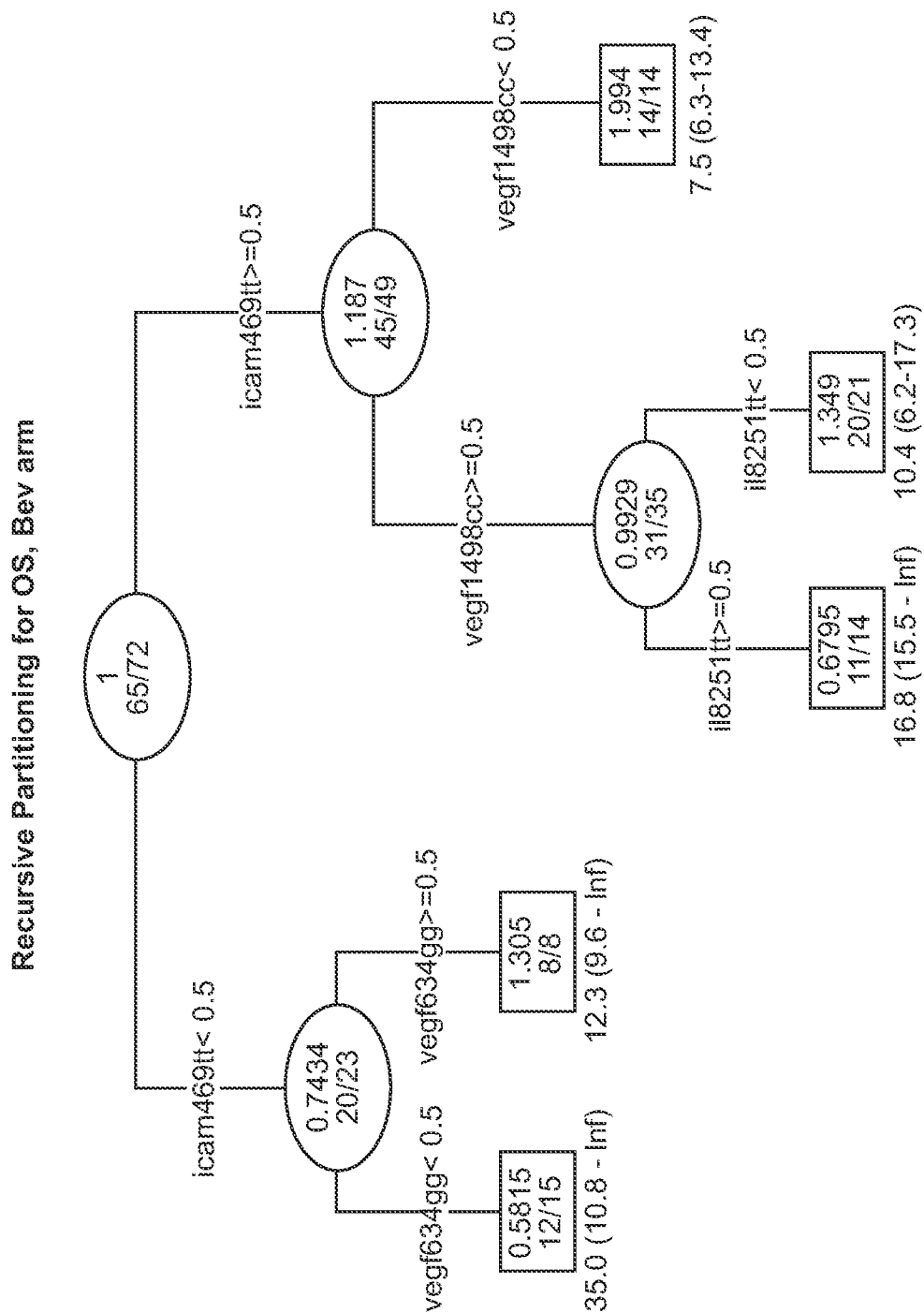


FIG. 1

Recursive Partitioning for PFS, Bev arm

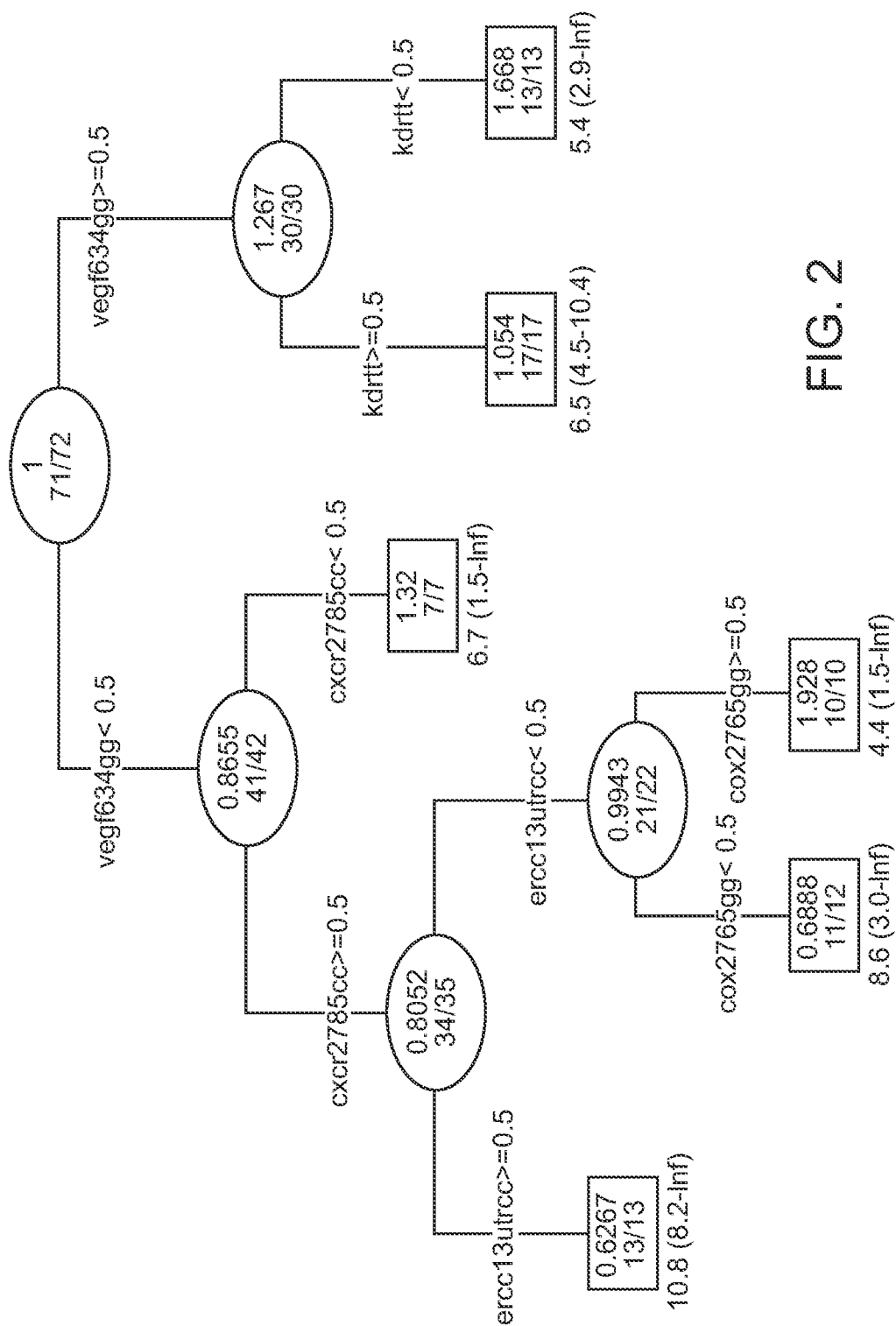


FIG. 2

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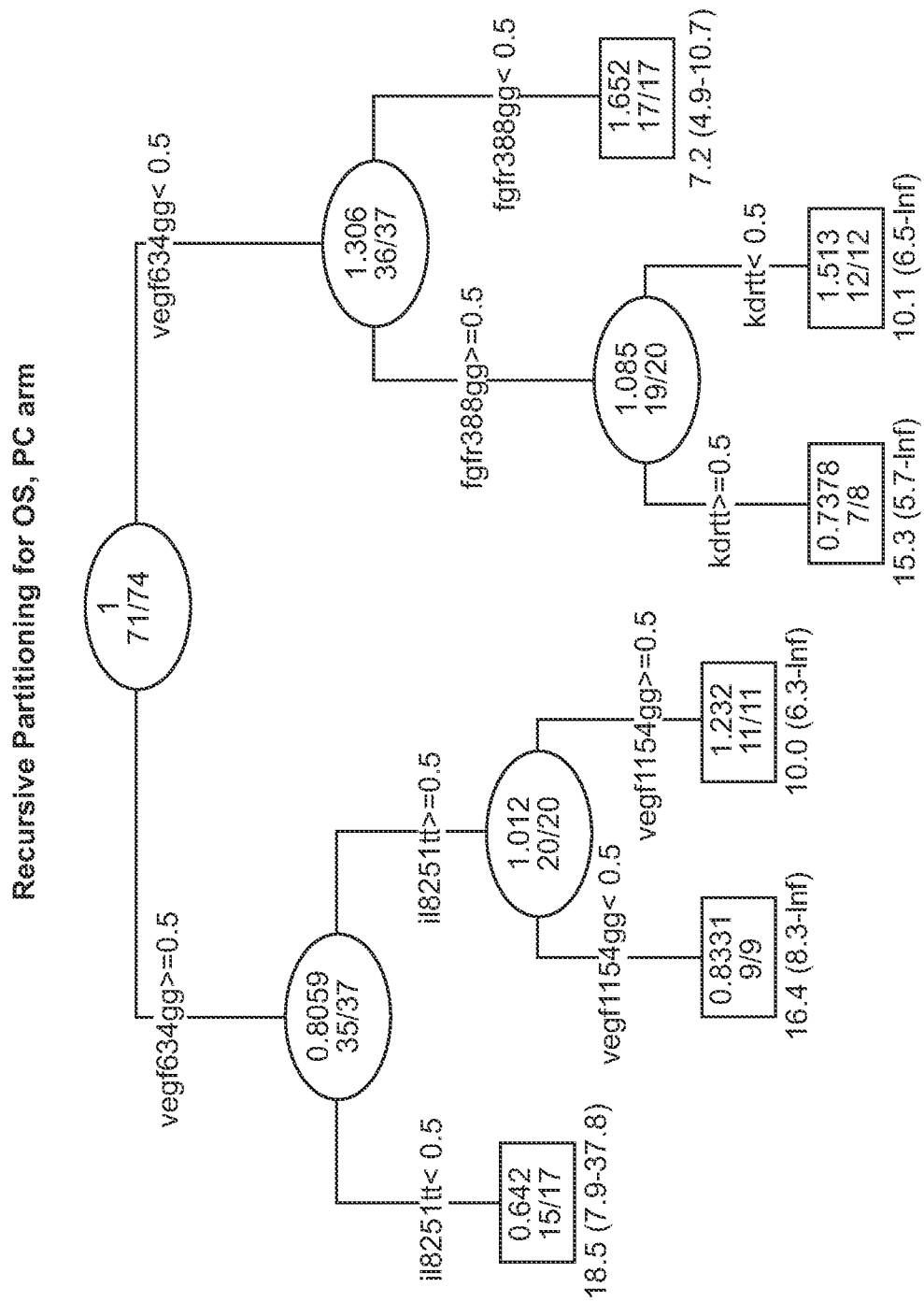


FIG. 3

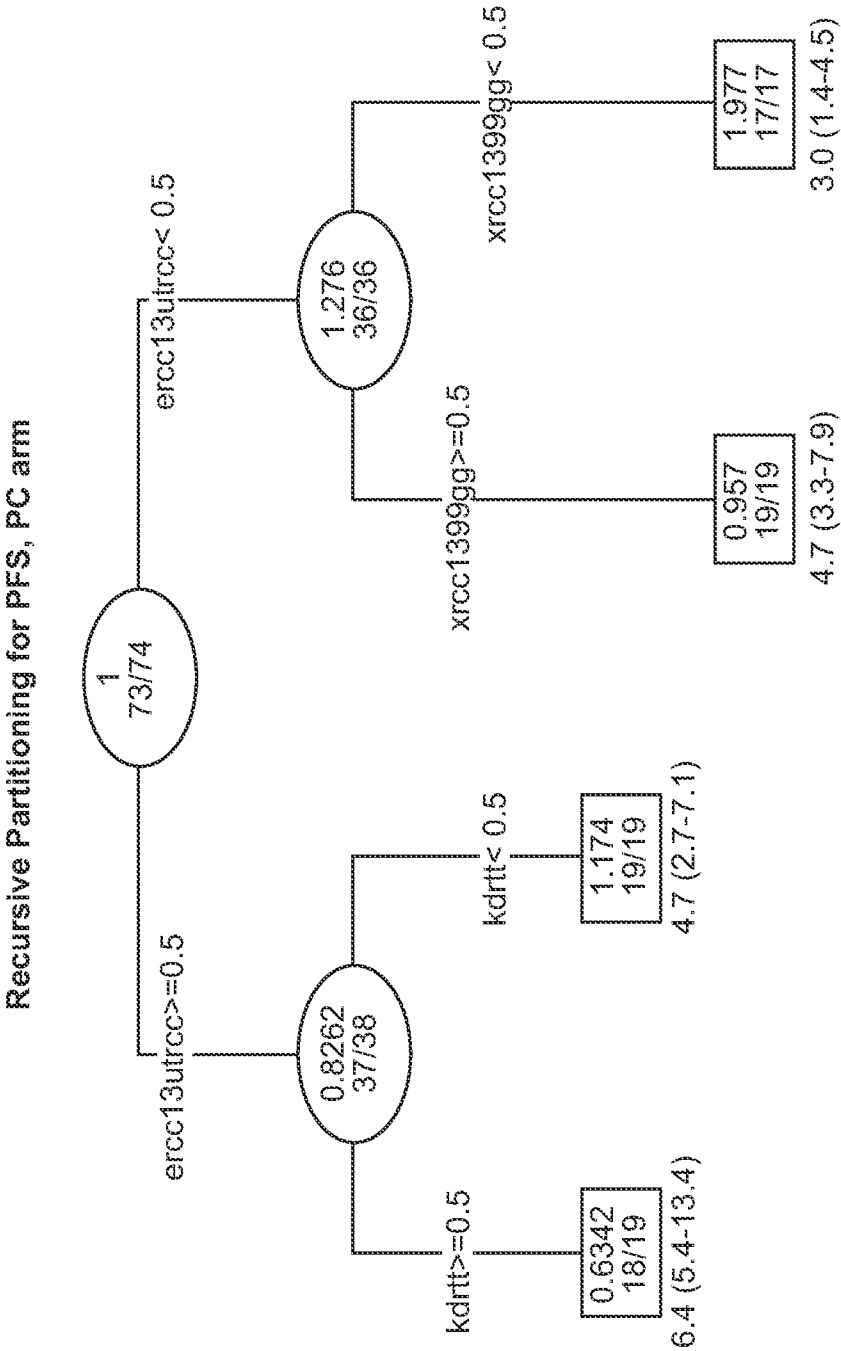


FIG. 4

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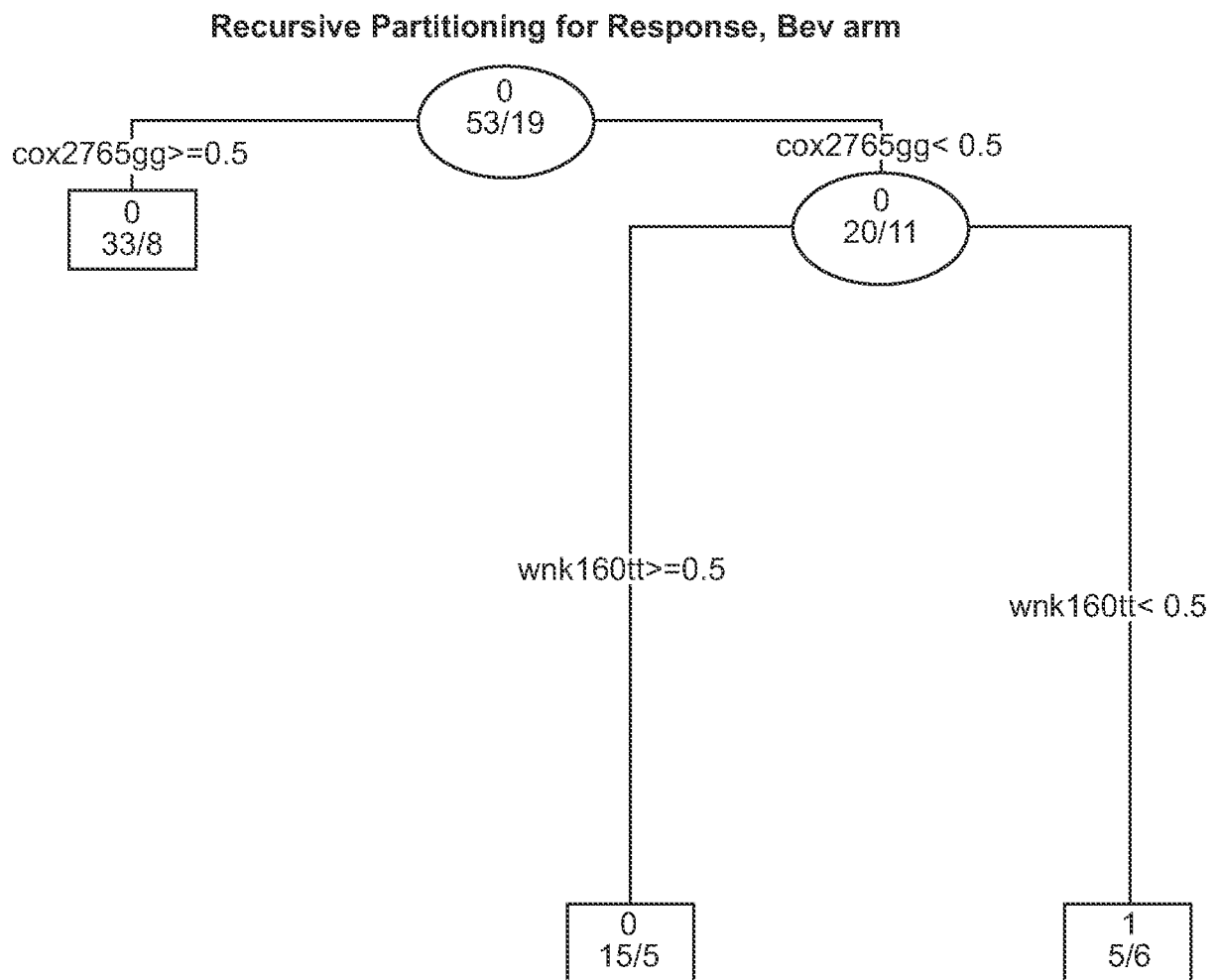
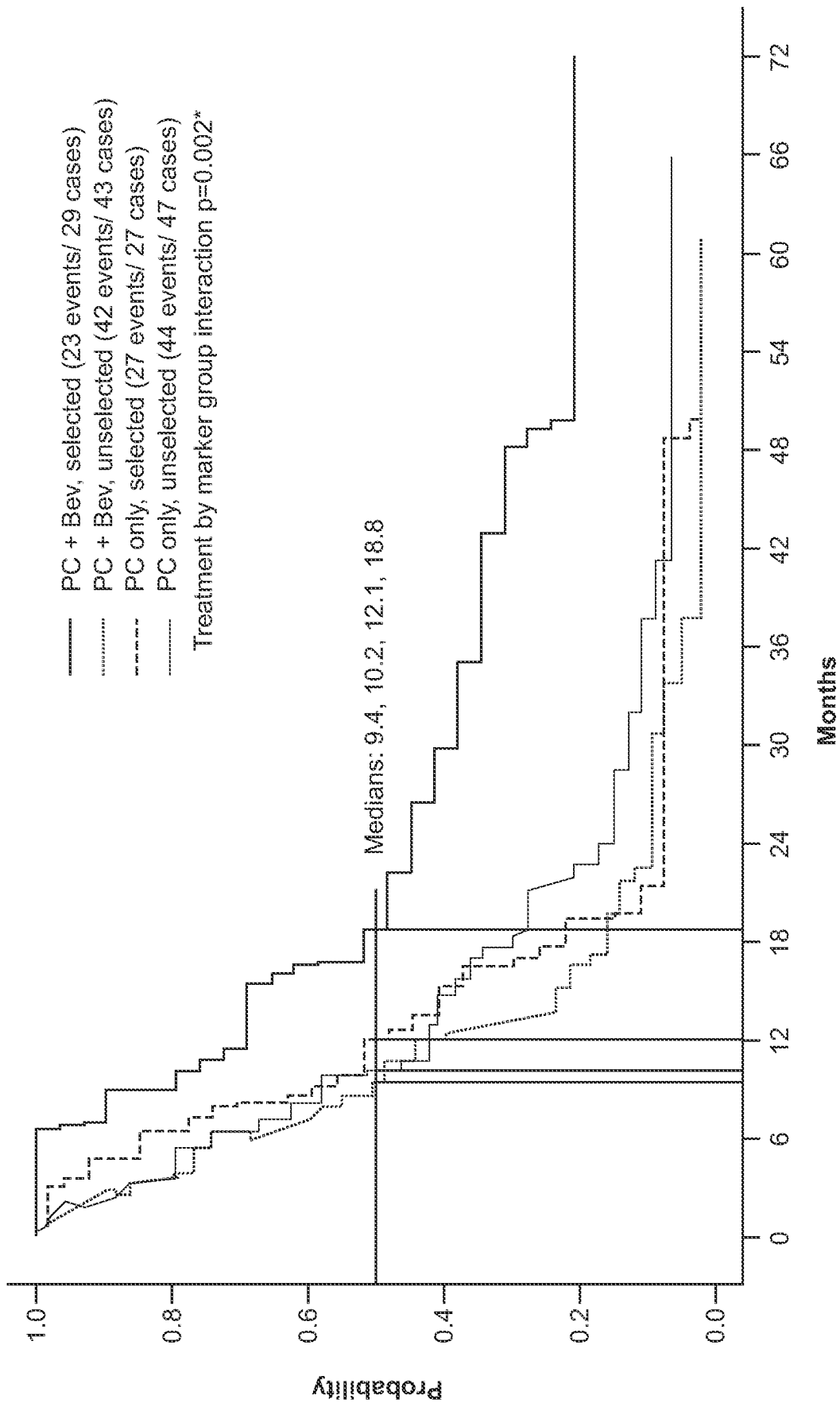


FIG. 5

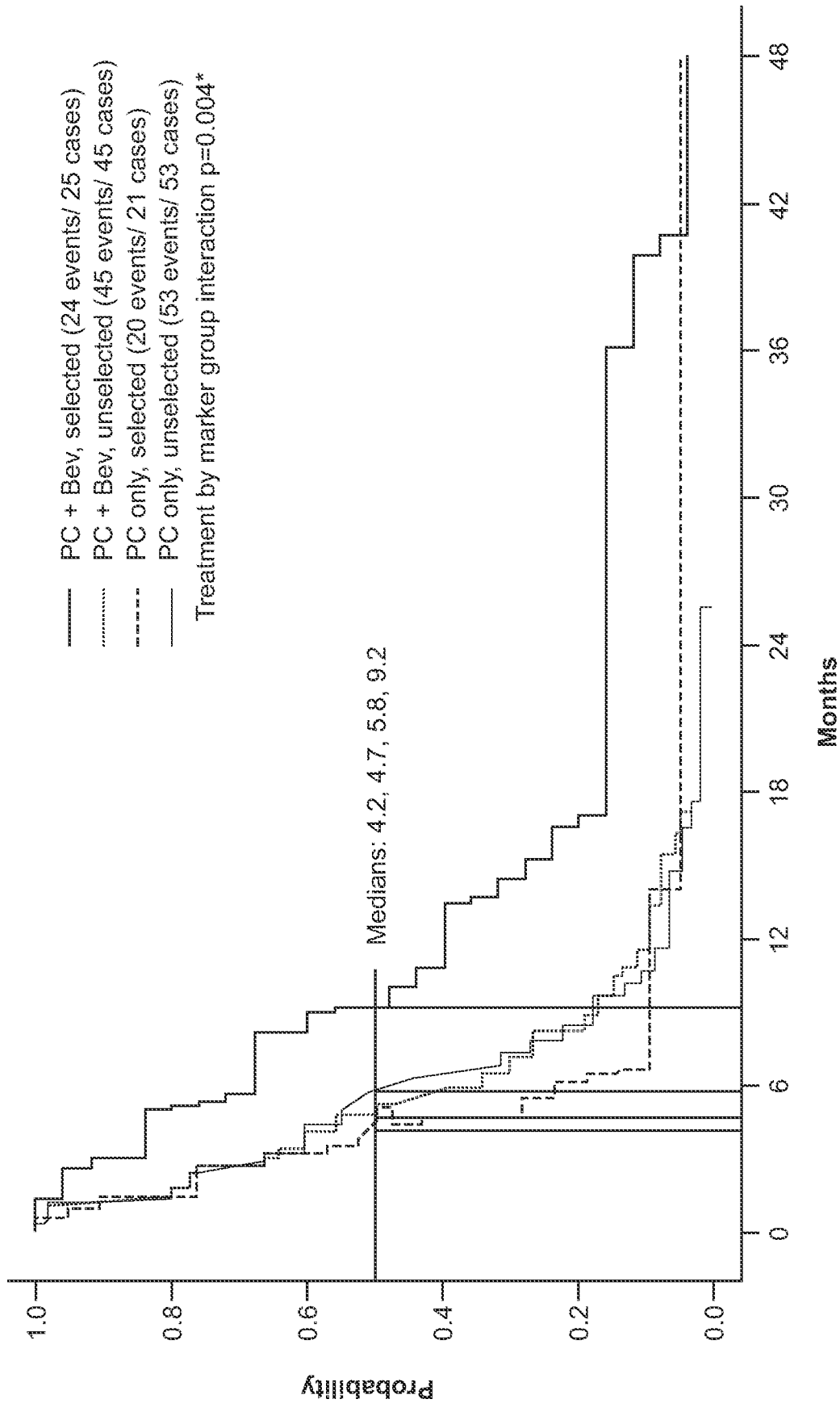
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*Cox model adjusted for treatment, marker group, gender, stage, weight loss, age<70, liver, bone, and adrenal metastases.

FIG. 6

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*Cox model adjusted for treatment, marker group, gender, stage, weight loss, age<70, liver, bone, and adrenal metastases.

FIG. 7

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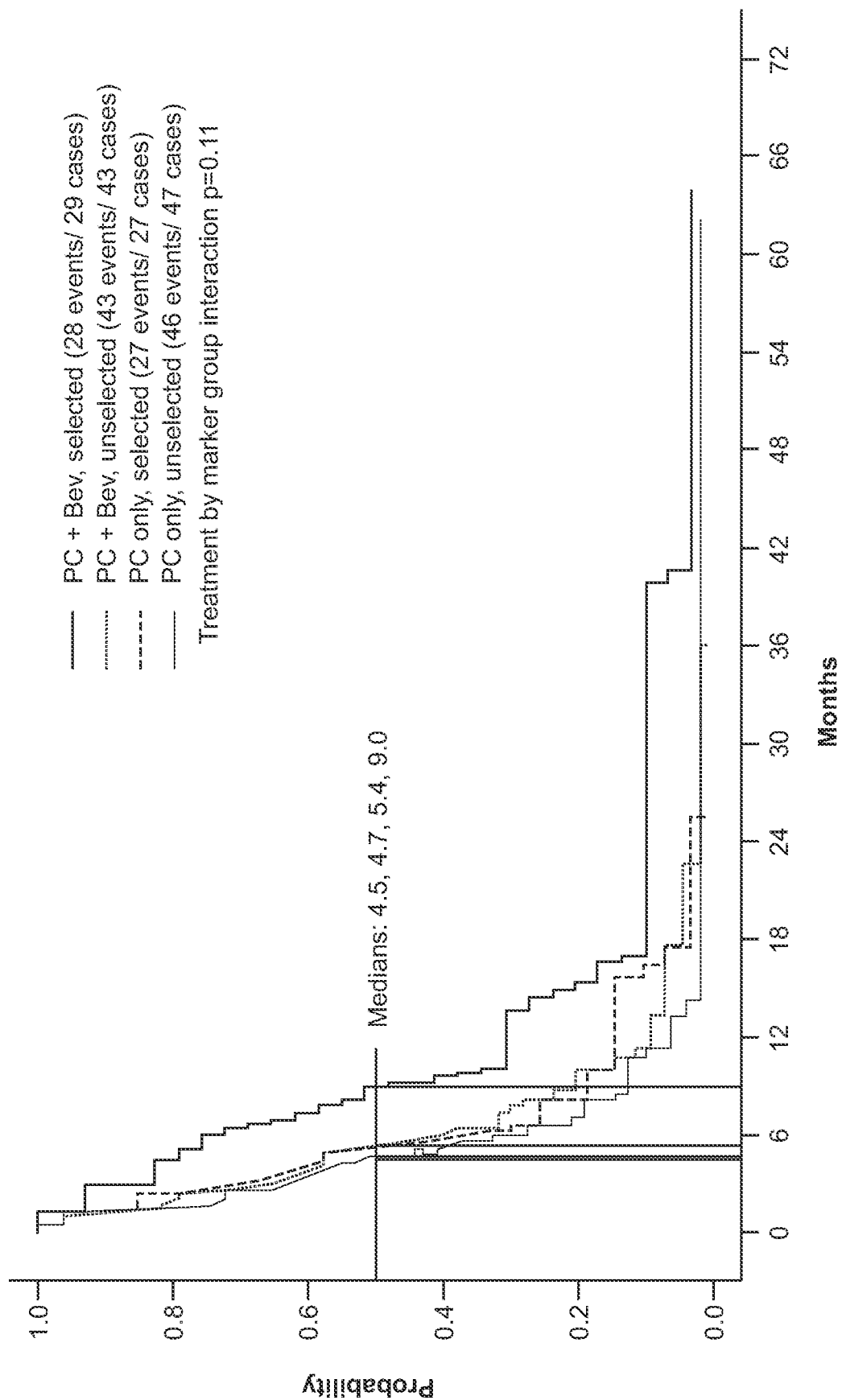


FIG. 8

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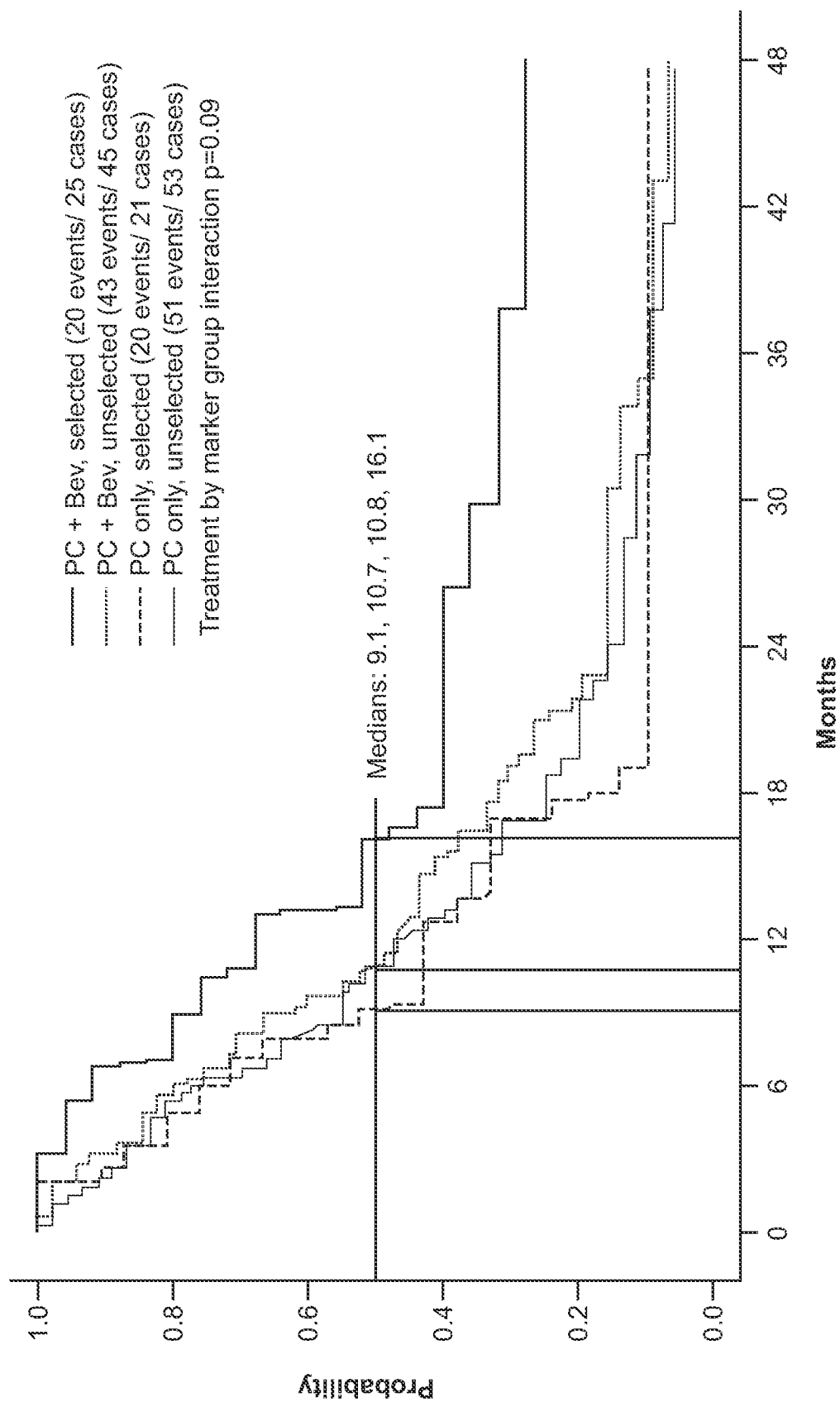


FIG. 9