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用於鑒別患者以使用醋酸阿比特龍治療的生物標誌物

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[73] Proprietor 專利所有人
Janssen Pharmaceutica NV
Turnhoutseweg 30
2340 Beerse
BELGIUM

[72] Inventor 發明人
Deborah SOKOL RICCI
Weimin LI
Michael GORMLEY
Jayaprakash KARKERA
Michael SCHAFFER

[74] Agent and / or address for service 代理人及/或送達地址
DEACONS
5th Floor, Alexandra House
Central
HONG KONG

(19) Europäisches Patentamt
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(73) Proprietor: **Janssen Pharmaceutica NV**
2340 Beerse (BE)

(72) Inventors:
- **SOKOL RICCI, Deborah**
  Raritan, New Jersey 08869 (US)
- **LI, Weimin**
  Spring House, Pennsylvania 19477 (US)
- **GORMLEY, Michael**
  Spring House, Pennsylvania 19477 (US)
- **KARKERA, Jayaprakash**
  Spring House, Pennsylvania 19477 (US)
- **SCHAFFER, Michael**
  Spring House, Pennsylvania 19477 (US)

(74) Representative: **Carpmaels & Ransford LLP**
One Southampton Row
London WC1B 5HA (GB)

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Description

TECHNICAL FIELD

[0001] Disclosed herein are methods of predicting a likelihood of longer survival following treatment with abiraterone acetate (AA) and prednisone in a patient having castration-resistant prostate cancer (CRPC).

BACKGROUND

[0002] Prostate cancer is the second most common cancer among men in the United States. It is also one of the leading causes of cancer death among men of all races and Hispanic origin populations. In 2010, 196,038 men in the United States were diagnosed with prostate cancer while 28,560 men in the United States died from prostate cancer. (U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999-2010 Incidence and Mortality Web-based Report. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2013.)

[0003] A number of therapeutic agents have been approved by the FDA for use in patients with metastatic castration-resistant prostate cancer (CRPC). Among these treatment options are docetaxel with prednisone, abiraterone acetate, cabazitaxel, enzalutamide, mitoxantrone, radium-223, sipuleucel-T, corticosteroids, and ketoconazole. As a result, clinicians and patients are challenged with a multitude of treatment options and potential sequencing of these agents that make clinical decision-making more complex. Methods for identification of therapies associated with improved survival and/or quality of life in particular patient subpopulations would facilitate such challenging decisions.

[0004] Mostaghel et al., Clin Cancer Res. 2011 Sep 15;17(18):5913-25 and Ripert et al., Prog Urol. 2013 Oct;23 Suppl 1:S16-22 describe studies relating to resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer. Hornberg et al., PLoS One. 2011 Apr 28;6(4):e19059 describes a study relating to the expression of androgen receptor splice variants in prostate cancer bone metastases. Sprenger et al., Horm Cancer. 2014 Aug;5(4):207-17 is a review examining a possible link between androgen receptor splice variants and castration-resistant prostate cancer. Heinrich et al., The Journal of Urology 2013 Apr;189(4) describes an analysis of up-regulated CYP17A1 expression under anti-androgen strategies in castration resistant prostate cancer.

SUMMARY

[0005] Provided herein is a method of predicting a likelihood of survival following treatment with abiraterone acetate (AA) in a human patient having castration-resistant prostate cancer (CRPC), the method comprising:

(a) contacting cDNA from a tumor sample of the patient obtained prior to treatment with abiraterone acetate (AA) with a gene chip, wherein said gene chip comprises probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) and proliferating cell nuclear antigen (PCNA);
(b) measuring an expression level of the at least one mRNA biomarker; and
(c) comparing the expression level of the at least one mRNA biomarker to an expression level of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA), or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA).

[0006] Also provided herein is a method of predicting a likelihood of survival following treatment with abiraterone acetate (AA) in a human patient having castration-resistant prostate cancer (CRPC), the method comprising:

(a) isolating RNA from a tumor sample of said patient;
(b) synthesizing cDNA from the RNA;
(c) measuring an expression level of at least one mRNA biomarker from the tumor sample, wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA) or any combination thereof, and wherein the expression level is measured by quantitative RT-PCR; and
(d) determining the relative expression of the at least one mRNA biomarker in relation to the expression of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA) or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free

survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA).

[0007] Also provided herein is abiraterone acetate (AA) for use in a method of treating castration-resistant prostate cancer (CRPC), the method comprising predicting a likelihood of survival following treatment with abiraterone acetate (AA) in a human patient by:

(a) contacting cDNA from a tumor sample of the patient obtained prior to treatment with abiraterone acetate (AA) with a gene chip, wherein said gene chip comprises probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) and proliferating cell nuclear antigen (PCNA);
(b) measuring an expression level of the at least one mRNA biomarker;
(c) comparing the expression level of the at least one mRNA biomarker to an expression level of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA), or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA); and
(d) if said patient has an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA) according to step (c), treating said patient with a therapeutically effective amount of abiraterone acetate (AA) and prednisone.

[0008] Also provided herein is abiraterone acetate (AA) for use in a method of treating castration-resistant prostate cancer (CRPC), the method comprising predicting a likelihood of survival following treatment with abiraterone acetate (AA) in a human patient by:

(a) isolating RNA from a tumor sample of said patient;
(b) synthesizing cDNA from the RNA;
(c) measuring an expression level of at least one mRNA biomarker from the tumor sample, wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA) or any combination thereof, and wherein the expression level is measured by quantitative RT-PCR;
(d) determining the relative expression of the at least one mRNA biomarker in relation to the expression of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA) or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA); and
(e) if said patient has an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA) according to step (d), treating said patient with a therapeutically effective amount of abiraterone acetate (AA) and prednisone.

[0009] Disclosed herein are methods of predicting a likelihood of survival following treatment with AA and prednisone in a patient having CRPC.

[0010] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the disclosed methods as defined in the appended claims. Other aspects will be apparent to those skilled in the art in view of the detailed description as provided herein.

DETAILED DESCRIPTION

[0011] The disclosed methods may be understood more readily by reference to the following detailed description taken in connection with the accompanying examples, which form a part of this disclosure. It is to be understood that the disclosed methods are not limited to the specific methods, conditions or parameters described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed methods. Also, as used in the specification including the appended claims, the singular forms "a," "an," and "the" include the plural, and reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. The term "plurality", as used herein, means more than one.

[0012] It is to be appreciated that certain features of the disclosed methods which are, for clarity, described herein in the context of separate embodiments may also be provided in combination in a single embodiment. Conversely, various features of the disclosed methods that are, for brevity, described in the context of a single embodiment may also be

provided separately or in any subcombination.

[0013] Provided herein are methods of predicting a likelihood of survival following treatment with AA in a patient having CRPC, the method comprising:

(a) contacting cDNA from a tumor sample of the patient obtained prior to treatment with AA with a gene chip, wherein said gene chip comprises probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) and proliferating cell nuclear antigen (PCNA);
(b) measuring an expression level of the at least one mRNA biomarker; and
(c) comparing the expression level of the at least one mRNA biomarker to an expression level of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA), or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with AA.

[0014] Also disclosed herein are methods of predicting a likelihood of survival following treatment with AA in a patient having CRPC, the method comprising:

(a) isolating RNA from a tumor sample of said patient;
(b) synthesizing cDNA from the RNA;
(c) measuring an expression level of at least one mRNA biomarker from the tumor sample, wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) and proliferating cell nuclear antigen (PCNA) or any combination thereof, and wherein the expression level is measured by quantitative RT-PCR; and
(d) determining the relative expression of the at least one mRNA biomarker in relation to the expression of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA), or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with AA.

[0015] As used herein, the term "patient" refers to any mammal having CRPC and whose sample can be analyzed with the disclosed methods. Thus, the disclosed methods are applicable to human and nonhuman subjects, although it is most preferably used for humans. The patient sample is a human sample. In other instances, the patient sample is a nonhuman sample. "Patient" and "subject" are used interchangeably herein.

[0016] As used herein, the phrase "castration-resistant prostate cancer" (CRPC) refers to prostate cancer that is no longer responsive to castration treatment (reduction of available androgen/testosterone/DHT by chemical or surgical means) but exhibits a reliance upon hormones for androgen receptor activation.

[0017] Those skilled in the art know that abiraterone acetate (referred to herein as "AA") is a 17a-hydroxylase/C17,20-lyase (CYP17) inhibitor that blocks androgen synthesis in the testes, adrenal gland, and prostate tumor.

[0018] As used herein, the term "survival" refers to radiographic progression free survival (rPFS), overall survival (OS), or a combination thereof. As used herein, the phrase "radiographic progression free survival" refers to the length of time during and after the treatment that the patient lives with CRPC, but wherein the CRPC does not get worse determined, for example, by monitoring lesions in bone, soft-tissue, or any combination thereof with x-ray, CT, MRI, or any combination thereof. As used herein, the phrase "overall survival" refers to the length of time from either the date of diagnosis of CRPC or the start of treatment that the patient remains alive, i.e. to death from any cause.

[0019] In some embodiments, the disclosed methods predict a likelihood of the length of time (during and after the treatment) that the patient will live with CRPC, but wherein the CRPC will not worsen. In other embodiments, the disclosed methods predict a likelihood of the length of time (from either the date of diagnosis of CRPC or the start of treatment) that the patient will remain alive. In yet other embodiments, the disclosed methods predict a likelihood of both.

[0020] As used herein, the phrase "at least one mRNA biomarker" refers to single mRNA biomarkers or mRNA biomarker groups (i.e. two or more associated biomarkers) which may be used as an indicator of patients having tumor subtypes that may respond better to therapy with AA and prednisone and/or that may be predictive of primary resistance (or response) to AA and prednisone in CRPC. Exemplary single mRNA biomarkers are listed in Table 1 and include, but are not limited to, ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, and UBE2C. Exemplary mRNA biomarker groups are listed in Table 1 and include, but are not limited to, CYP17A1 and cofactors (CYB5A, CYP17A1, CYP3A5, DUSP5, HNF1A, NR0B1, and POR) group, androgen controlled group (AKR1C3, FKBP5, and PCNA), and multivariate panel (AR, CYP21A2/CYP21A1P, HLA-A, IGJ, KRT17, LCN2, and PCNA).

Table 1 - Exemplary single mRNA biomarkers and mRNA biomarker groups

mRNA Biomarker	Name	GenBank Accession No.
Single mRNA Biomarker		
ANLN	Anillin, actin binding protein	NM_018685.2
HSD17B10	Hydroxysteroid (17-beta) dehydrogenase 10	NM_001037811.2
NUSAP1	Nucleolar and spindle associated protein 1	NM_001243142.1
SF1	Splicing factor 1 (SF1), transcript variant 6	NM_001178030.1
UBE2C	Ubiquitin-conjugating enzyme E2C	NM_001281741.1
SRD5A1	Steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)	NM_001047.2
mRNA Biomarker Groups		
Androgen controlled		
- AKR1C3	Aldo-keto reductase family 1, member C3	NM_001253908.1
- FKBP5	FK506 binding protein 5	NM_001145775.1
- PCNA	Proliferating cell nuclear antigen	NM_002592.2
CYP17A1 and Cofactors		
- CYP17A1	Cytochrome P450, family 17, subfamily A	NM_000102.3
- CYB5A	Cytochrome b5 type A (microsomal)	NM_001914.3
- POR	P450 (cytochrome) oxidoreductase (POR)	NM_000941.2
- CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	NM_000777.3
- DUSP5	Dual specificity phosphatase 5	NM_004419.3
- HNF1A	Transcription factor 1, hepatic; LF-B1, hepatic nuclear factor	NM_000545.3
- NR0B 1	Nuclear receptor subfamily 0, group B, member 1	NM_000475.4
Multivariate panel group		
- AR	Androgen receptor	NM_000044.3
- CYP21A2; CYP21A1P	Cytochrome P450, family 21, subfamily A, polypeptide 2; Cytochrome P450, family 21, subfamily A, polypeptide 1 pseudogene	NM_000500.7
- HLA-A	Major histocompatibility complex, class I, A	NM_001242758.1
- IGJ	Immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	NM_144646.3
- KRT17	Keratin 17	NM_000422.2
- LCN2	Lipocalin 2	NM_005564.3
- PCNA	Proliferating Cell Nuclear Antigen	NM_002592.2

[0021] The "at least one mRNA biomarker" comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) and proliferating cell nuclear antigen (PCNA), sometimes referred to herein as an androgen controlled group. In some instances of the disclosure, the "at least one mRNA biomarker" refers to one or more single mRNA biomarkers including, but not limited to, ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, or any combination

thereof. In other instances, the "at least one mRNA biomarker" refers to one or more mRNA biomarker groups including, but not limited to, CYP17A1 and cofactors group, androgen controlled group (which is a required feature of the claims), multivariate panel, or any combination thereof. For example, in some aspects of the methods the CYP17A1 and cofactors group comprises CYB5A, CYP17A1, CYP3A5, DUSP5, HNF1A, NR0B1, and POR. In the claimed embodiments, the androgen controlled group comprises AKR1C3, FKBP5, and PCNA. In some aspects of the methods, the multivariate panel comprises AR, CYP21A2/CYP21A1P, HLA-A, IGJ, KRT17, LCN2, and PCNA. In other instances, the "at least one mRNA biomarker" refers to one or more single mRNA biomarkers in addition to one or more mRNA biomarker groups including, but not limited to, ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, CYP17A1 and cofactors group, androgen controlled group (which is a required feature of the claims), multivariate panel, or any combination thereof.

[0022] As used herein, the phrase "contacting cDNA ... with a gene chip" refers to a procedure whereby cDNA derived from a patient's tumor sample is incubated with, or added to, a gene chip in order to evaluate gene expression.

[0023] In some instances, the gene chip comprises probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, CYP17A1 and cofactors group, androgen controlled group (which is a required feature of the claims), multivariate panel, or any combination thereof. In other instances, the gene chip consists essentially of probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, CYP17A1 and cofactors group, androgen controlled group (which is a required feature of the claims), multivariate panel or any combination thereof. In yet other instances, the gene chip consists of probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, CYP17A1 and cofactors group, androgen controlled group (which is a required feature of the claims), multivariate panel or any combination thereof.

[0024] Those skilled in the art know that numerous procedures are available for measuring an expression level of the at least one mRNA biomarker including, but not limited to, quantitative RT-PCR, microarray, RNA sequencing, Nanostring, or any combination thereof.

[0025] As used herein, "reference gene" refers to one or more housekeeping genes including, but not limited to, GAPDH, Hs99999905_m1, ACTB, Hs99999903_m1, or any combination thereof.

[0026] In some embodiments, the expression level of the reference gene comprises a geometric mean of housekeeping genes. In such embodiments, comparing the expression level of the at least one mRNA biomarker to an expression level of a reference gene can comprise comparing the level of expression of the at least one mRNA biomarker to the geometric mean of the housekeeping genes. For example, expression values of single mRNA biomarkers can be calculated using the comparative CT method as described in Schmittgen TD, Livak KJ. Analyzing real-time PCR data by the comparative CT method. Nature Protocols. 2008; 3:1101-1108. Briefly, a normalization factor can be calculated for each sample using a geometric mean of housekeeping genes. Relative expression values of all other transcripts can be quantified as the difference between the CT and the normalization factor. Transcript expression can then be calculated by the negation of the relative expression values to account for the inverse relationship between expression and CT (this is equivalent to the log 2 transform of 2^(-DeltaCT)).

[0027] In other embodiments, comparing the expression level of a biomarker group to an expression level of a reference gene can comprise genewise normalization and summarization of member genes in the biomarker group. For example, the expression level of a biomarker group can first be normalized using the comparative CT method as discussed above and a summarized score can be derived for the biomarker group by computing the median of z-scores (e.g. transformed values obtained by subtracting the mean expression from the expression in a sample, and dividing by the standard deviation of the expression) of member genes in the biomarker group.

[0028] In other embodiments, a multivariate panel of biomarkers can be derived using penalized regression of time to event data. A set of data can be used to specify model parameters and select informative biomarkers via cross-validation. For an individual with biomarker expression X, the risk of experiencing an event relative to the average patient is given by $\exp(X\beta)$, where β is the log hazard ratio defined based on the association of biomarker expression with time to event in the data used to define the model and exp is the exponential function. In this manner, each individual patient's relative risk can be predicted on the basis of biomarker expression. Relative risk can be evaluated as a continuous index of the probability that the patient will experience a survival event or it can be dichotomized to indicate low and high risk groups of patients.

[0029] In some embodiments, an increase in the expression level of the ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, CYP17A1 and cofactors group, androgen controlled group, or any combination thereof in the patient sample relative to the expression level of the reference gene is indicative of increased rPFS, OS, or a combination thereof.

[0030] Disclosed herein are methods of predicting a likelihood of survival following treatment with AA in a patient having CRPC, the method comprising:

(a) contacting cDNA from a tumor sample of the patient obtained prior to treatment with AA with a gene chip, wherein said gene chip comprises probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, CYP17A1 and cofactors group, androgen controlled

group (which is a required feature of the claims) or any combination thereof;
(b) measuring an expression level of the at least one mRNA biomarker;
(c) comparing the expression level of the at least one mRNA biomarker to an expression level of a reference gene, wherein an increase in the expression level of the ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, CYP17A1 and cofactors group, androgen controlled group (which is a required feature of the claims), or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with AA; and
(d) treating said patient with a therapeutically effective amount of AA and prednisone.

[0031] In some instances, a decrease in the expression level of the multivariate panel group in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival for said patient following treatment with AA.

[0032] Disclosed herein are methods of predicting a likelihood of survival following treatment with AA in a patient having CRPC, the method comprising:

(a) contacting cDNA from a tumor sample of the patient obtained prior to treatment with AA with a gene chip, wherein said gene chip comprises probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises multivariate panel group;
(b) measuring an expression level of the at least one mRNA biomarker;
(c) comparing the expression level of the at least one mRNA biomarker to an expression level of a reference gene, wherein a decrease in the expression level of the multivariate panel group in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival for said patient following treatment with AA; and
(d) treating said patient with a therapeutically effective amount of AA and prednisone.

[0033] In some instances, an increase in the expression level of the ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, or CYP17A1 and cofactors group, or androgen controlled group (which is a required feature of the claims) in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with AA, and a decrease in the expression level of the multivariate panel group in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival for said patient following treatment with AA.

[0034] In some embodiments, increased rPFS and/or OS is indicated by an increase in the expression level of the at least one mRNA biomarker relative to the median expression value of the at least one mRNA biomarker from a patient population. Exemplary median expression values are provided in Table 4, herein. In other instances, increased rPFS and/or OS is indicated by any level of increase in the expression of ANLN, HSD17B10, NUSAP1, SF1, SRD5A1, UBE2C, or CYP17A1 and cofactors group, or androgen controlled group (which is a required feature of the claims) or a decrease in the expression level of the multivariate panel group relative to the reference gene. For example, and without intent to be limiting, the Hazard Ratios (HRs) exemplified in Table 3 indicate the strength of the association between the relative expression of the at least one mRNA biomarker and outcome (e.g. rPFS or OS). Therefore, a unit increase in the relative expression of ANLN, for example, reduces the hazard of rPFS event by 16 percent (i.e. 1-0.84 = 0.16). Because the expression values of the at least one mRNA biomarker were log2 transformed, a unit of change equates to a 2-fold difference relative to the expression level of the reference gene.

[0035] Numerous procedures are known for isolating RNA from a tumor sample including, but not limited to, commercially available kits such as AllPrep DNA/RNA FFPE Kit from Qiagen and the Ambion Recoverall kit. Additionally, one skilled in the art would know how to synthesize cDNA from the isolated RNA, including, but not limited to, the use of Life Technologies High Capacity cDNA Reverse Transcription Kit.

[0036] As used herein, "treating" comprises administering to a patient a therapeutically effective dose of AA and prednisone such that the CRPC and/or the associated symptoms are reduced, ameliorated, alleviated, reversed, inhibited, prevented and/or eliminated. Treating also encompasses a reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage caused by CRPC.

[0037] In some embodiments, AA (CB7630) and prednisone are co-administered. For example, AA and prednisone may be administered sequentially in either order or contemporaneously.

[0038] The "therapeutically effective dose of AA and prednisone" will be dependent on several factors including, but not limited to, stage and severity of the CRPC, as well as other factors relating to the health of the patient. Those skilled in the art would know how to determine the therapeutically effective dose.

[0039] In some embodiments, the patient exhibiting increased expression of the at least one mRNA biomarker may have nonmetastatic or early stage CRPC. In other embodiments, the patient exhibiting increased expression of the at

least one mRNA biomarker may have metastatic or late stage CRPC.

EXAMPLES

Study Design

[0040] COU-AA-302 is a Phase 3, multinational, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of AA and prednisone (AA+P) to placebo and prednisone (Placebo+P) in medically or surgically castrated asymptomatic or mildly symptomatic men with mCRPC who have not received cytotoxic chemotherapy. Patients were assigned in a 1:1 ratio to receive either AA+P or Placebo+P and were stratified based on ECOG performance status of 0 or 1, as discussed in Clinical Study Protocol: A Phase 3 Randomized, Double-blind, Placebo-controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects with Metastatic Castration Resistant Prostate Cancer. Protocol COU-AA-302; EudraCT No. 2008-008004-41; 09 Jul 2012.

[0041] All subjects in Study COU-AA-302, regardless of treatment group, received concurrent prednisone. See Clinical Study Report: CSR COU-AA-302 2012. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer. Issue Date: 26 October 2012. Subjects who received AA+P are referred to herein as the "AA group" and in tables as "AA." Subjects who received Placebo+P are referred to herein as the "Placebo group" and in tables as "Placebo." Additional study related details can be obtained from the COU-AA-302 clinical study protocol or clinical study report.

Biomarker Sample Collection and Processing

[0042] Formalin fixed paraffin embedded (FFPE) tumor samples from 258 subjects who optionally consented for RNA analysis were collected and shipped to the central laboratory (Covance, IN) for RNA analysis. FFPE samples from 152 subjects had sufficient RNA for TaqMan® Low Density Array (TLDA) analysis. Samples from the other 106 subjects were excluded either due to lack of tumor or low RNA yield. Of the 152 samples evaluated by TLDA, samples from 42 subjects were excluded from data analysis due to technical failures (no detectable gene expression or batch effects induced by microdissection of samples with low tumor content or low RNA input mass [< 250 ng of total RNA]). The remaining evaluable samples from 110 subjects (Biomarker population) who were part of the ITT population (10%) and who had drug exposure with clinical data for at least one of the efficacy endpoints (rPFS, OS) were included in the analysis. Samples from these subjects were included in the mRNA analysis using the TaqMan® array microfluidic cards.

[0043] Ninety-six mRNAs were selected for gene expression profiling, including CYP17A1 and cofactors (CYP17, P450 reductase, and cytochrome b5) along with AR and its splice variants (AR full length, AR V7, and AR567ES). Also included in the analysis were genes representing major biological pathways including androgen signaling, proliferation, cell growth, immune response, and steroidogenic genes.

Methods for Sample Analysis

RNA extraction

[0044] The RNA from FFPE samples was extracted by the central laboratory (Covance Genomics Laboratory, Seattle, WA) initially using the AllPrep DNA/RNA FFPE Kit from Qiagen as per manufacturer's instructions. To improve the yield of RNA in samples that failed extraction procedures due to the low RNA yield, Ambion Recoverall kit was used for remaining samples. RNA samples were treated with DNase according to manufacturer's recommendation and RNA quantity was measured via RiboGreen.

cDNA synthesis, pre-amplification, and microarray

[0045] cDNA synthesis was performed using Life Technologies High Capacity cDNA Reverse Transcription Kit with RNase Inhibitor (Catalog Number 4374967) according to the vendor's protocol with the following minor modification: a 30ul reaction volume was used in place of 20ul. Total RNA of 250 ng was used for the cDNA synthesis with the exception of a subset of samples with low RNA yield (150 ng of total RNA was used), but these samples were subsequently excluded from statistical analysis due to batch effect.

[0046] Preamplification was performed using Life Technologies TaqMan® PreAmp Master Mix Kit (Catalog Number 4384267) according to the vendor's protocol. TaqMan® Array Microfluidic Cards from Applied Biosystems were used for RNA analysis and run according to the vendor's protocol. The card was run on an ABI 7900 HT System.

Table 2 - DNA sequences of primers used to assay the expression of biomarkers

Biomarker	Primer Sequence	Region*
mRNA Biomarker		
ANLN	CCAAGGCTATTACTCCAAAGCGACTC CTCACATCTATAACCACAAAAAGCAA CATTCATTCTTCAGTCATGG	2909-2980
HSD17B10	GACCTCTGAGAAGGATGTGCAAACAG CTCTGGCTCTAGCAAAAGGAAAGTTT GGCCGTGTGGATGTAGCTGTCAACT	226-302
NUSAP1	GTCAGGTTTTCAGCTGCTACTAAAGA TAATGAGCATAAGCGTTCACTGACCA AGACTCCAGCCAGAAAGTCTGCACAT GTGACCGTGT	1102-1189
SF1	TCCCCTTCCCCTGAGCCCATCTACAAT AGCGAGGGGAAGCGGCTTAACACCC GAGAGTTCCGCACCCGCAAAAAGCTG GAAGAGGAGCGGCACAACCTCATCA CAGAGATGGTTGCAC	687-804
UBE2C	TTAAGAAGTACCTGCAAGAAACCTAC TCAAAGCAGGTCACCAGCCAGGAGCC CTGACCCAGGCTG	464-528
SRD5A1	CGGTGCTTAATTTACCCATTTCTGATG CGAGGAGGAAAGCCTATGCCACTGTT GGCGTGTACAATGGCGATTATGT	482-557
mRNA Biomarker Groups		
Androgen controlled		
- AKR1C3	TTGCTAGCCACCCTAATTATCCATATT CAGATGAATATTAACATGGAGGGCTT TGCCTGATGTCTACCAGAAGCCCTGT GTGTGGATGGTGACGCAGAGGACGTC TCTATGCC	978-1090
- FKBP5	CAAGGAAGAGGCCAATAAAGCAATG GGCAAGAAGACTTCAGAAGGGGTCA CTAATGAAAAAGGAACAGACAGTCA AGCAATG	1579-1660
- PCNA	AACCAGGAGAAAGTTTCAGACTATGA AATGAAGTTGATGGATTTAGATGTTG AACAACTTGGAATTCCAGAACAGGAG TACAGCTGTGTAGTAAAGATGCCTTC TGGTGAATTTGCACGTATATGCCGAG ATCTCAGCC	558-696

(continued)

CYP17A1 and Cofactors		
- CYP17A1	CAGCATCGGTGAGTTTGCTGTGGACA AGGGCACAGAAGTTATCATCAATCTG TGGGCGCTGCATCACAATGAG	1309-1381
- CYB5A	TGACAGACCAAAGTTAAACAAGCCTC CGGAACCTTAAAGGCGGTGTTTCAAG GAAACTCTTATCACTACTATTGATTCT AGTTCCAGTTGGTGGACCAACTGGGT GATCCCTGCCATCTCTGCAGTGGCCG TCGCCTTGATGTAT	402-546
- POR	GCCGACCTGAGCAGCCTGCCAGAGAT CGACAACGCCCTGGTGGTTTTCTGCA TGGCCACCTACGGTGAGGGAGACCCC ACCGACAATGCCCAGGACTTCTACGA CTGGCTGCAGG	449-563
- CYP3A5	GGGGAACGTATGAAGGTCAACTCCCT GTGCTGGCCATCACAGATCCCGACGT GATCAGAACAGTGCTAGTGAAAGAAT GTTAT	317-399
- DUSP5	AGGGGGATATGAGACTTTCTACTCGG AATATCCTGAGTGTTGCGTGGATGTA AAACCCATTTCACAAGAGAAGATTGA GAGTGAGAGAGCCCTCATCAGCCAGT GTGG	633-740
- HNF1	CACCCATGCAGGGCAGGGAGGGCTG ATTGAAGAGCCCACAGGTGATGAGCT ACCAACCAAGAAGGGGCGGAGGAAC CGTTTCAAGTGGGGCCCAGCA	554-650
- NR0B 1	ACCCGGACGTGCCGGGCCTGCAGTGC GTGAAGTACATTCAGGGACTCCAGTG GGGAACTCAGCAAATACTCAGTGAAC ACACCAGGATGACGCACCAAGGGCC CCATGACAGATTCATCGAACTTAATA GTACCCTTTTC CTGCTG	1178-1323
Multivariate panel group		
- AR	GCTTCCGCAACTTACACGTGGACGAC CAGATGGCTGTCATTCAGTACTCCTGG ATGGGGCTCATGGTGTTTG	3289-3360

(continued)

Multivariate panel group		
- CYP21A2; CYP21A1P	GTGAGCGCATGAGAGCCCAGCCCGGC ACCCCTGTGGCCATTGAGGAGGAATT CTCTCTCCTCACCTGCAGCATCATCTG TTACCTCACCTTCGGAGACAAGATCA AGGACGACAACTTAAT	550-671
- HLA-A	CTGCAAGCAGTGACAGTGCCCAGGGC TCTGATGTGTCTCTCACAGCTTGTAAA GTGTGAGACAGCTGCCT	1034-1104
- IGJ	TGTTCCTCTGAACAACAGGGAGAATA TCTCTGATCCCACCTCACCATTGAGAA CCAGATTTGTGTACCATTTGTCTGACC TCTGTAAAAAATGTGATCCTACAGAA GTGGAGCTGGA	330-447
- KRT17	GAACAAGATCCTCACAGCCACCGTGG ACAATGCCAACATCCTGCTACAGATT GACAATGCCCGTCTGGCTGCTGATGA CTTCCGCACCAAGTT	547-640
- LCN	TCCCAATCGACCAGTGTATCGACGGC TGAGTGCACAGGTGCCGCCAGCTGCC GCACCAGCC	642-703
- PCNA	AACCAGGAGAAAGTTTCAGACTATGA AATGAAGTTGATGGATTTAGATGTTG AACAACTTGGAATTCCAGAACAGGAG TACAGCTGTGTAGTAAAGATGCCTTCT GGTGAATTTGCACGTATATGCCGAGA TCTCAGC	558-696
* The region indicates the bases in the target transcript that comprise the primer region.		

Data normalization

[0047] Raw CT values were filtered to remove values greater than 30. Quadruple replicate CT values were summarized using the geometric mean. Expression values were calculated using the comparative CT method as described in Schmittgen TD, Livak KJ. Analyzing real-time PCR data by the comparative Ct method. Nature Protocols. 2008; 3:1101-1108. Briefly, a normalization factor was calculated for each sample using the geometric mean of housekeeping genes (ACTB and GAPDH). Relative expression values of all other transcripts were quantified as the difference between CT and the normalization factor. Transcript expression was calculated by the negation of the relative expression values to account for the inverse relationship between expression and CT. This is equivalent to the log 2 transform of 2^(-DeltaCT).

Statistical Analysis

[0048] All statistical tests were interpreted at 5% significance levels (two-sided). For determination of specificity of biomarker association with clinical endpoints in AA group, a $P < 0.05$ in the AA group and a $P \geq 0.2$ in the placebo group is required. Demographics and baseline characteristics were compared between the biomarker population and the ITT population using ANOVA (continuous variables) or Chi-Square (categorical variables) tests.

[0049] Biomarker data received from the central laboratory was processed in the following order:

- Four samples with below lower limit of quantification (LLOQ) for all biomarkers were excluded.
- Seven biomarkers for which at least 95% of the sample data were missing or below LLOQ were also excluded.
- For subjects with duplicate samples, which were generated using the same extraction methodology, laser capture microdissection (LCM) methodology, and RNA input mass, the average value was used.
- Results below LLOQ for a biomarker were imputed by half of the minimum of all available values for the same biomarker. All biomarker values were then log2-transformed.
- For analysis of biomarker groups, the median of normalized values from all biomarkers in a biomarker group was used to determine the composite score for each subject by first calculating z-score for each biomarker's imputed and log2-transformed value across all subjects using (Biomarker value - mean across all subjects) / (standard deviation across all subjects) and then summarizing the z-scores of all genes in each group by the median value to generate a biomarker group composite score.

[0050] Association of these data with clinical endpoints (rPFS by Independent Review (IND), rPFS by Investigative Review (INV), and OS) were analyzed as follows:

- Cox regression was conducted as the main analysis method with baseline ECOG score (randomization stratification factor) and each biomarker value (continuous) or composite score for biomarker group (continuous) in the model for each treatment group and for the total biomarker population.
- To correct for RNA extraction method, Cox regression was conducted with baseline ECOG score, RNA extraction method (Qiagen AllPrep or Ambion RecoverAll) and each biomarker value (continuous) or composite score for biomarker group (continuous) in the model for each treatment group and for the total biomarker population.
- Dichotomized biomarker data by median (≥ median or < median) were used in Cox regression that was conducted for each treatment group and for the total biomarker population.
- Treatment group comparison was performed in biomarker subpopulation defined by dichotomized biomarker data based on median using Cox regression.
- Relevant p values (type III), HR, and 95% confidence intervals are presented for each association in the data tables.
- For biomarkers with the highest significance (consistent association with multiple clinical endpoints), the Kaplan-Meier method was used to estimate the distribution of rPFS and OS.

Biomarker Results

Demographics and Baseline Characteristics

[0051] The biomarker population was generally representative of the overall ITT population in the COU-AA-302 study (Data not shown). However, the biomarker population had a higher frequency of subjects with previous surgeries and included a higher percentage of subjects outside of North America. No statistically significant differences for other demographic and baseline characteristics were observed.

Frequency of Gene Expression

[0052] Of the 94 mRNA biomarkers tested, 87 non-housekeeping mRNAs had expression in at least 5% of the samples. The number of tumors with detectable expression values varied for each gene (Data not shown). Notably, AR full length was detected in all tumors tested, while AR V7 was detectable in 65.5% of samples and AR567ES expression was not observed in any of the subjects (Data not shown). The frequency of CYP17 detectable expression was 30.9% (Data not shown).

Association Analysis of Biomarkers with rPFS (Independent review) - Single mRNA Biomarker

[0053] Association analysis of single mRNA biomarker expression values with rPFS (IND) was evaluated using Cox regression within each treatment group or in the treatment groups combined. Baseline ECOG scores and the randomization stratification factor were included in the model. The biomarkers that showed consistent association with rPFS by IND and other clinical endpoints are summarized in Table 3.

[0054] Out of 94 mRNA biomarkers examined, eight biomarkers showed significant association with rPFS (IND) in the AA group ($p<0.05$), but not in the Placebo group ($p \geq 0.2$), indicating that the expression of these biomarkers may be predictive of AA efficacy (Data not shown). These biomarkers included: CYP17 cofactors (HNF1A); AR regulated genes (KLK3), proliferation markers (ANLN, NUSAP1, UBE2C); an enzyme in the "backdoor" synthesis of dihydrotestosterone (DHT), HSD17B10; an enzyme in the conversion pathway of C19 steroids, SRD5A1; and pre-mRNA splicing factor SF1. After correcting for the RNA extraction methodology in a multivariate Cox regression model, ANLN (HR=0.86; p=0.0413),

HSD17B10 (HR=0.78; p=0.0396), NUSAP1 (HR=0.78; p=0.0272), and SRD5A1 (HR=0.79; p=0.0360) remained significantly associated with rPFS(IND) in the AA group and UBE2C showed a trend of association with rPFS (IND) in the AA group (HR=0.88; p=0.0584).

[0055] Association of biomarkers with rPFS (IND) was also evaluated using Cox regression with biomarker expression dichotomized into binary variables using the median expression as a cutpoint. The results were similar to the analysis done with treating biomarker data as continuous variables (Data not shown).

Association Analysis of Biomarkers with rPFS (Independent review) -mRNA Biomarker Group

[0056] Association of biomarker composite scores with rPFS (IND) was evaluated by Cox regression stratified by ECOG scores. One biomarker group, "androgen controlled genes" that included AKR1C3, FKBP5, and PCNA, was significantly associated with rPFS (IND) in the AA group, but not in the Placebo group before (HR=0.57 [0.37, 0.88]; p=0.0115) and after (HR=0.63 [0.39,0.99], p=0.0467) correcting for RNA methodology, suggesting an association with efficacy to AA treatment. Additionally, CYP17A1 and cofactors group (CYB5A, CYP17A1, CYP3A5, DUSP5, HNF1A, NR0B1, POR; HR=0.43 [0.21,0.89]; p=0.0224) also showed significant association with rPFS (IND) in the AA group but not in the Placebo group. (See Table 3)

Association Analysis of Biomarkers with rPFS (Investigator review) - Single mRNA Biomarker

[0057] Association of single mRNA biomarkers with rPFS (INV) was evaluated using the same method as for rPFS (IND). Twelve biomarkers were associated with rPFS in the AA group but not in the Placebo group (Data not shown). Of these, five biomarkers - HSD17B10, SF1, UBE2C, NUSAP1, and SRD5A1 - were associated with both rPFS (IND) and rPFS (INV). (See Table 3).

Association Analysis of Biomarkers with rPFS (Investigator review) -mRNA Biomarker Group

[0058] Association of biomarker groups with rPFS (INV) were evaluated using the same method as for rPFS (IND). Four biomarker groups were associated with rPFS in the AA group, but not in the Placebo group (Data not shown). Of these, two biomarker groups, androgen controlled genes (HR=0.58; p=0.0220) and proliferation pathway module (HR=0.63; p=0.0133) were associated with both rPFS (IND) and rPFS (INV).

Association Analysis of Biomarkers with OS - Single mRNA Biomarker

[0059] Association of single mRNA biomarkers with OS was evaluated using the same method as for rPFS (IND). Eleven biomarkers were associated with OS in the AA group, but not in the Placebo group (Data not shown). Of these, SF1 was associated with both rPFS (rPFS IND: HR=0.82; p=0.0214; rPFS INV: HR=0.78; p=0.0095) and OS (HR=0.67 [0.50,0.89]; p= 0.0066).

Association Analysis of Biomarkers with OS - mRNA Biomarker Group

[0060] Association of biomarker groups with OS was evaluated using the same method as for rPFS (IND). Five biomarker groups were associated with OS in the AA group, but not in the Placebo group (Data not shown). Of these, two biomarker groups, androgen controlled genes (rPFS IND: HR=0.57; p=0.0115; OS: HR=0.31; p=0.0037) and CYP17A1 and cofactors (rPFS IND: HR=0.43; p=0.0224; OS: HR=0.20; p=0.0156) were associated with both rPFS and OS.

Table 3. Association of mRNA biomarkers with rPFS(IND) and rPFS(INV) within each treatment group

			AA	Placebo	
	Endpoint	**P value**	**HR**	**P value**	**HR**
mRNA Biomarker					
MRNA10(ANLN-Hs01122612_m1)	rPFS (IND)	0.014	0.84 (0.72,0.96)	0.6693	0.97 (0.82,1.13)
	rPFS (INV)	0.0032	0.80 (0.69,0.93)	0.3146	0.93 (0.80,1.07)
MRNA40(HSD17B10-Hs00189576_m1)	rPFS (IND)	0.0343	0.78 (0.62,0.98)	0.3271	0.90 (0.73,1.11)

(continued)

			AA	Placebo	
	Endpoint	**P value**	**HR**	**P value**	**HR**
mRNA Biomarker					
	rPFS (INV)	0.0124	0.76 (0.62,0.94)	0.3911	0.92 (0.75,1.12)
MRNA70(NUSAP1-Hs01006195_m1)	rPFS (IND)	0.0491	0.82 (0.67,1.00)	0.7724	1.03 (0.85,1.25)
	rPFS (INV)	0.0119	0.78 (0.64,0.95)	0.2736	0.91 (0.76,1.08)
MRNA81(SF1-Hs00190309_m1)	rPFS (IND)	0.0214	0.82 (0.69,0.97)	0.6734	0.97 (0.82,1.13)
	rPFS (INV)	0.0095	0.78 (0.64,0.94)	0.9223	1.01 (0.86,1.18)
MRNA82(SRD5A1-Hs00971643_g1)	rPFS (IND)	0.0337	0.80 (0.65,0.98)	0.228	0.87 (0.70,1.09)
	rPFS (INV)	0.0468	0.83 (0.68,1.00)	0.3152	0.90 (0.74,1.10)
MRNA92(UBE2C-Hs00964100_g1)	rPFS (IND)	0.0213	0.85 (0.74,0.98)	0.9156	1.01 (0.85,1.20)
	rPFS (INV)	0.0022	0.81 (0.71,0.93)	0.2194	0.91 (0.78,1.06)
mRNA biomarker groups					
GP03(CYP17A1 and cofactors)	rPFS (IND)	0.0224	0.43 (0.21,0.89)	0.8164	1.07 (0.59,1.94)
	rPFS (INV)	0.3002	0.71 (0.37,1.36)	0.9498	1.02 (0.56,1.84)
GP08(androgen controlled)	rPFS (IND)	0.0115	0.57 (0.37,0.88)	0.201	1.26 (0.88,1.81)
	rPFS (INV)	0.022	0.58 (0.37,0.92)	0.6608	1.08 (0.78,1.49)
Biomarkers or biomarker groups associated with rPFS in the AA group (P<0.05) but not in the placebo arm (P>=0.2). Association of biomarker expression with rPFS in AA or placebo group is determined using cox regression. P-value indicates the significance of the association. Hazard Ratio (HR) indicates the magnitude of the association					

Summary Statistics

[0061] Summary statistics including the number of observations (N), the average and standard deviation of expression, the median expression, first and third quartiles and minimum and maximum expression level for each biomarker are shown in Table 4.

Table 4. Summary statistics of mRNA biomarkers

	N	**Mean (sd)**	**Median**	**Q1, Q3**	**Min, Max**
mRNA Biomarker					
MRNA10(ANLN-Hs01122612_m1)	110	-0.06 (2.13)	0.05	-1.76,1.62	-5.75,5.22
MRNA40(HSD17B10-Hs00189576_m1)	110	0.91 (1.57)	1.25	-0.17,2.03	-3.08,4.26
MRNA70(NUSAP1-Hs01006195_m1)	110	-2.28 (1.75)	-2.18	-3.46,-0.89	-6.80,1.80
MRNA81(SF1-Hs00190309_m1)	110	-2.11 (1.78)	-1.82	-3.02,-0.93	-6.85,0.99
MRNA82(SRD5A1-Hs00971643_g1)	110	-0.46 (1.84)	-0.36	-1.59,0.69	-4.99,6.99
MRNA92(UBE2C-Hs00964100_g1)	110	-0.11 (2.17)	0.24	-2.01,1.49	-5.82,4.78
mRNA Biomarker Groups					
GP03(CYP17A1 and cofactors)	110	-0.09 (0.55)	-0.13	-0.49,0.18	-1.23,1.78

(continued)

mRNA Biomarker Groups					
GP08(androgen controlled)	110	0.01 (0.81)	0.24	-0.39,0.58	-1.54,1.79

[0062] Coefficients were derived from Cox regression model of biomarker expression and baseline ECOG status against time to radiographic progression free survival. Table 5 provides model parameters for each marker. Using these values, expression of the biomarker and baseline ECOG status can be translated into relative risk of rPFS.

Table 5. Regression coefficients for survival models

Marker	Marker. Coef	BLECOG. Coef
GP03(CYP17A1 and cofactors)	-0.836	-1.379
GP08(androgen controlled)	-0.562	-1.545
MRNA10(ANLN-Hs01122612_m1)	-0.180	-1.561
MRNA40(HSD17B10-Hs00189576_m1)	-0.249	-1.536
MRNA70(NUSAP1-Hs01006195_m1)	-0.203	-1.605
MRNA81(SF1-Hs00190309_m1)	-0.204	-1.559
MRNA82(SRD5A1-Hs00971643_g1)	-0.224	-1.596
MRN A92(UBE2C-Hs00964100_g 1)	-0.161	-1.601

Optimization and validation of multivariate AA response biomarkers

[0063] A multivariate biomarker panel was identified using penalized regression to define a classifier that predicts radiographic progression free survival. The model was defined using an elastic net approach for feature selection and model specification. Data was separated into training and testing sets using a 70%-30% split. Within the training data, 10-fold cross-validation was used to define model parameters. Elastic net models have two parameters: alpha and lambda. Alpha is the elastic net penalty and determines the specific mixture of penalties that will be applied to limit complexity of the model. Lambda is the regularization penalty which determines the magnitude of the parameter used to limit complexity. After optimizing alpha and lambda using cross-validation, the values were used to define the cox regression model on the training data. The model is used to predict the relative risk of progression free-survival for all subjects in the training set. Then, time-dependent ROC analysis was used to determine the predictive power of the model and dichotomize the relative risk into two groups associated with low and high risk at the timepoint at which 90% of subjects with radiographic progression had observed recurrence of disease (t = 20.48 months). This model, consisting of regression coefficients, timepoint and cutoff to discriminate between low and high risk, was applied to predict the relative risk of subjects in the independent test data and evaluate the predictive power and association with time to event of the classifier. This evaluation is repeated on the placebo data to confirm that the classifier is predictive of response to Abiraterone and not prognostic of outcome independent of treatment. Features used in the model building process included all single gene markers detected in greater than 50% of samples to exclude low expressing genes. The model was optimized to alpha = 0.5 and lambda = 0.209. Using these parameters, the optimized survival models were defined as described in Table 6.

Table 6. Optimized multivariate model based on expression of all single gene markers measured in > 50% of subjects.

Marker	Beta *
MRNA12(AR-Hs00171172_m1)	0.226
MRNA26(CYP21A2;CYP21A1P-Hs00365734 _g1)	0.062
MRNA37(HLA-A-Hs01058806 _g1)	0.03
MRNA50(IGJ-Hs00376160_m1)	0.18
MRNA57(KRT17-Hs01588578_m1)	0.02

(continued)

Marker	Beta *
MRNA59(LCN2-Hs01008571_m1)	0.039
MRNA71(PCNA-Hs00427214_g1)	0.241
* Beta indicates the optimized regression coefficient for the associated marker.	

[0064] Table 7 lists the predictive metrics which describe the performance of these models on the independent test and placebo group data.

Table 7. Predictive metrics of optimized multivariate model based on expression of all single gene markers measure in > 50% of subjects.

Data	Timepoint	KM	AUC
Test	20.48134	0.474	0.778
Placebo	20.48134	0.262	0.627
Data indicates the dataset used i.e. independent test set or placebo data. KM indicates the Kaplan-Meier survival estimate at time t. AUC indicates the area under the ROC curve at time t.			

[0065] Table 8 lists the statistics describing the association between classifier predictions and time to radiographic progression free survival.

Table 8. Association of predictive model with time to radiographic progression free survival

Data	Cutpoint	Timepoint	Risk	Event/ Total (Perc)	Median (95CI)	HR (95CI)	P(Cox)	P(KM)
Test	0.9977	20.4813	Low	6/15 (40.0)	- (13.8,-)	-	-	-
			High	4/4 (100.0)	8.2 (1.8,-)	6.25 (1.54,25.34)	0.0104	0.0035
Placebo	0.9977	20.4813	Low	29/43 (67.4)	11.0 (8.3,13.8)	-	-	-
			High	3/5 (60.0)	8.3 (1.7,-)	0.97 (0.30,3.20)	0.9654	0.9652

Claims

1. A method of predicting a likelihood of survival following treatment with abiraterone acetate (AA) in a human patient having castration-resistant prostate cancer (CRPC), the method comprising:

   (a) contacting cDNA from a tumor sample of the patient obtained prior to treatment with abiraterone acetate (AA) with a gene chip, wherein said gene chip comprises probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) and proliferating cell nuclear antigen (PCNA);
   (b) measuring an expression level of the at least one mRNA biomarker; and
   (c) comparing the expression level of the at least one mRNA biomarker to an expression level of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA), or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of

progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA).

2. A method of predicting a likelihood of survival following treatment with abiraterone acetate (AA) in a human patient having castration-resistant prostate cancer (CRPC), the method comprising:

(a) isolating RNA from a tumor sample of said patient;
(b) synthesizing cDNA from the RNA;
(c) measuring an expression level of at least one mRNA biomarker from the tumor sample, wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA) or any combination thereof, and wherein the expression level is measured by quantitative RT-PCR; and
(d) determining the relative expression of the at least one mRNA biomarker in relation to the expression of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA) or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA).

3. The method of any one of the previous claims, wherein the expression level of the at least one mRNA biomarker is increased relative to the median expression value of the at least one mRNA biomarker from a patient population.

4. The method of any one of the previous claims, wherein the human patient has non-metastatic or early stage castration-resistant prostate cancer (CRPC).

5. The method of any one of claims 2 to 4, wherein the human patient having castration-resistant prostate cancer (CRPC) has not received cytotoxic chemotherapy.

6. The method of any one of the previous claims wherein the method further comprises a step of selecting said patient for treatment with a therapeutically effective amount of abiraterone acetate (AA) and prednisone for treating said patient.

7. Abiraterone acetate (AA) for use in a method of treating castration-resistant prostate cancer (CRPC), the method comprising predicting a likelihood of survival following treatment with abiraterone acetate (AA) in a human patient by:

(a) contacting cDNA from a tumor sample of the patient obtained prior to treatment with abiraterone acetate (AA) with a gene chip, wherein said gene chip comprises probes for at least one mRNA biomarker, and wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) and proliferating cell nuclear antigen (PCNA);
(b) measuring an expression level of the at least one mRNA biomarker;
(c) comparing the expression level of the at least one mRNA biomarker to an expression level of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA), or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA); and
(d) if said patient has an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA) according to step (c), treating said patient with a therapeutically effective amount of abiraterone acetate (AA) and prednisone.

8. Abiraterone acetate (AA) for use in a method of treating castration-resistant prostate cancer (CRPC), the method comprising predicting a likelihood of survival following treatment with abiraterone acetate (AA) in a human patient by:

(a) isolating RNA from a tumor sample of said patient;
(b) synthesizing cDNA from the RNA;
(c) measuring an expression level of at least one mRNA biomarker from the tumor sample, wherein the at least one mRNA biomarker comprises aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA) or any combination thereof, and wherein the expression

level is measured by quantitative RT-PCR;
(d) determining the relative expression of the at least one mRNA biomarker in relation to the expression of a reference gene, wherein an increase in the expression level of the aldo-keto reductase family 1 member C3 (AKR1C3), FK506 binding protein 5 (FKBP5) or proliferating cell nuclear antigen (PCNA) or any combination thereof in the patient sample relative to the expression level of the reference gene indicates an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA); and
(e) if said patient has an increased likelihood of progression free survival, overall survival, or both for said patient following treatment with abiraterone acetate (AA) according to step (d), treating said patient with a therapeutically effective amount of abiraterone acetate (AA) and prednisone.

9. The abiraterone acetate for use of any one of claims 7 or 8, wherein the expression level of the at least one mRNA biomarker is increased relative to the median expression value of the at least one mRNA biomarker from a patient population.

10. The abiraterone acetate for use of any one of claims 7 to 9, wherein the human patient has non-metastatic or early stage castration-resistant prostate cancer (CRPC).

11. The abiraterone acetate for use of any one of claims 8 to 10, wherein the human patient having castration-resistant prostate cancer (CRPC) has not received cytotoxic chemotherapy.

Patentansprüche

1. Verfahren zur Vorhersage einer Überlebenswahrscheinlichkeit nach Behandlung mit Abirateronacetat (AA) bei einem menschlichen Patienten mit kastrationsresistentem Prostatakrebs (CRPC), wobei das Verfahren Folgendes umfasst:

(a) Inkontaktbringen von cDNA aus einer Tumorprobe des Patienten, die vor der Behandlung mit Abirateronacetat (AA) erhalten wurde, mit einem Genchip, wobei der Genchip Sonden für mindestens einen mRNA-Biomarker umfasst und wobei der mindestens eine mRNA-Biomarker Aldo-Keto-Reduktase-Familie-1-Mitglied C3 (AKR1C3), FK506-Bindungsprotein 5 (FKBP5) und Proliferating-Cell-Nuclear-Antigen (PCNA) umfasst;
(b) Messen eines Expressionsniveaus des mindestens einen mRNA-Biomarkers; und
(c) Vergleichen des Expressionsniveaus des mindestens einen mRNA-Biomarkers mit einem Expressionsniveau eines Referenzgens, wobei eine Erhöhung des Expressionsniveaus des Aldo-Keto-Reduktase-Familie-1-Mit-glieds C3 (AKR1C3), FK506-Bindungsproteins 5 (FKBP5) oder Proliferating-Cell-Nuclear-Antigen (PCNA) oder einer beliebigen Kombination davon in der Patientenprobe relativ zum Expressionsniveau des Referenzgens eine erhöhte Wahrscheinlichkeit des progressionsfreien Überlebens, des Gesamtüberlebens, oder beider, für den Patienten nach Behandlung mit Abirateronacetat (AA) anzeigt.

2. Verfahren zur Vorhersage einer Überlebenswahrscheinlichkeit nach Behandlung mit Abirateronacetat (AA) bei einem menschlichen Patienten mit kastrationsresistentem Prostatakrebs (CRPC), wobei das Verfahren umfasst:

(a) Isolieren von RNA aus einer Tumorprobe des Patienten;
(b) Synthetisieren von cDNA aus der RNA;
(c) Messen eines Expressionsniveaus von mindestens einem mRNA-Biomarker aus der Tumorprobe, wobei der mindestens eine mRNA-Biomarker Aldo-Keto-Reduktase-Familie-1-Mitglied C3 (AKR1C3), FK506-Bindungsprotein 5 (FKBP5) oder Proliferating-Cell-Nuclear-Antigen (PCNA) oder eine beliebige Kombination davon umfasst, und wobei das Expressionsniveau durch quantitative RT-PCR gemessen wird; und
(d) Bestimmen der relativen Expression des mindestens einen mRNA-Biomarkers in Bezug auf die Expression eines Referenzgens, wobei eine Erhöhung des Expressionsniveaus des Aldo-Keto-Reduktase-Familie-1-Mitglieds C3 (AKR1C3), FK506-Bindungsproteins 5 (FKBP5) oder Proliferating-Cell-Nuclear-Antigen (PCNA) oder einer beliebigen Kombination davon in der Patientenprobe im Verhältnis zum Expressionsniveau des Referenzgens eine erhöhte Wahrscheinlichkeit des progressionsfreien Überlebens, des Gesamtüberlebens oder beider für den Patienten nach Behandlung mit Abirateronacetat (AA) anzeigt.

3. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Expressionsniveau des mindestens einen mRNA-Biomarkers relativ zum medianen Expressionswert des mindestens einen mRNA-Biomarkers aus einer Patienten-

population erhöht ist.

4. Verfahren nach einem der vorhergehenden Ansprüche, wobei der menschliche Patient nicht-metastasierten oder kastrationsresistenten Prostatakrebs (CRPC) im Frühstadium hat.

5. Verfahren nach einem der Ansprüche 2 bis 4, wobei der menschliche Patient mit kastrationsresistentem Prostatakrebs (CRPC) keine zytotoxische Chemotherapie erhalten hat.

6. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Verfahren ferner einen Schritt zum Auswählen des Patienten für die Behandlung mit einer therapeutisch wirksamen Menge von Abirateronacetat (AA) und Prednison zum Behandeln des Patienten umfasst.

7. Abirateronacetat (AA) zur Verwendung in einem Verfahren zur Behandlung von kastrationsresistentem Prostatakrebs (CRPC), wobei das Verfahren die Vorhersage einer Überlebenswahrscheinlichkeit nach Behandlung mit Abirateronacetat (AA) bei einem menschlichen Patienten umfasst durch:

(a) Inkontaktbringen von cDNA aus einer Tumorprobe des Patienten, die vor der Behandlung mit Abirateronacetat (AA) erhalten wurde, mit einem Genchip, wobei der Genchip Sonden für mindestens einen mRNA-Biomarker umfasst und wobei der mindestens eine mRNA-Biomarker Aldo-Keto-Reduktase-Familie-1-Mitglied C3 (AKR1C3), FK506-Bindungsprotein 5 (FKBP5) und Proliferating-Cell-Nuclear-Antigen (PCNA) umfasst;
(b) Messen eines Expressionsniveaus des mindestens einen mRNA-Biomarkers; und
(c) Vergleichen des Expressionsniveaus des mindestens einen mRNA-Biomarkers mit einem Expressionsniveau eines Referenzgens, wobei eine Erhöhung des Expressionsniveaus des Aldo-Keto-Reduktase-Familie-1-Mitglieds C3 (AKR1C3), FK506-Bindungsprotein 5 (FKBP5) oder Proliferating-Cell-Nuclear-Antigen (PCNA) oder einer beliebigen Kombination davon in der Patientenprobe im Verhältnis zum Expressionsniveau des Referenzgens eine erhöhte Wahrscheinlichkeit des progressionsfreien Überlebens, des Gesamtüberlebens, oder beider, für den Patienten nach Behandlung mit Abirateronacetat (AA) anzeigt; und
(d) wenn der Patient eine erhöhte Wahrscheinlichkeit des progressionsfreien Überlebens, des Gesamtüberlebens oder beider für den Patienten nach Behandlung mit Abirateronacetat (AA) gemäß Schritt (c) aufweist, Behandeln des Patienten mit einer therapeutisch wirksamen Menge Abirateronacetat (AA) und Prednison.

8. Abirateronacetat (AA) zur Verwendung in einem Verfahren zum Behandeln von kastrationsresistentem Prostatakrebs (CRPC), wobei das Verfahren die Vorhersage einer Überlebenswahrscheinlichkeit nach Behandlung mit Abirateronacetat (AA) bei einem menschlichen Patienten umfasst durch:

(a) Isolieren von RNA aus einer Tumorprobe des Patienten;
(b) Synthetisieren von cDNA aus der RNA;
(c) Messen eines Expressionsniveaus von mindestens einem mRNA-Biomarker aus der Tumorprobe, wobei der mindestens eine mRNA-Biomarker Aldo-Keto-Reduktase-Familie-1-Mitglied C3 (AKR1C3), FK506-Bindungsprotein 5 (FKBP5) oder Proliferating-Cell-Nuclear-Antigen (PCNA) oder eine beliebige Kombination davon umfasst, und wobei das Expressionsniveau durch quantitative RT-PCR gemessen wird;
(d) Bestimmen der relativen Expression des mindestens einen mRNA-Biomarkers in Bezug auf die Expression eines Referenzgens, wobei eine Erhöhung des Expressionsniveaus des Aldo-Keto-Reduktase-Familie-1-Mitglieds C3 (AKR1C3), FK506-Bindungsprotein 5 (FKBP5) oder Proliferating-Cell-Nuclear-Antigen (PCNA) oder einer beliebigen Kombination davon in der Patientenprobe im Verhältnis zum Expressionsniveau des Referenzgens eine erhöhte Wahrscheinlichkeit des progressionsfreien Überlebens, des Gesamtüberlebens oder beider für den Patienten nach Behandlung mit Abirateronacetat (AA) anzeigt; und
(e) wenn der Patient eine erhöhte Wahrscheinlichkeit des progressionsfreien Überlebens, des Gesamtüberlebens oder beider für den Patienten nach Behandlung mit Abirateronacetat (AA) gemäß Schritt (d) aufweist, Behandeln des Patienten mit einer therapeutisch wirksamen Menge Abirateronacetat (AA) und Prednison.

9. Abirateronacetat zur Verwendung nach einem der Ansprüche 7 oder 8, wobei das Expressionsniveau des mindestens einen mRNA-Biomarkers relativ zum medianen Expressionswert des mindestens einen mRNA-Biomarkers aus einer Patientenpopulation erhöht ist.

10. Abirateronacetat zur Verwendung nach einem der Ansprüche 7 bis 9, wobei der menschliche Patient nicht-metastasierten oder kastrationsresistenten Prostatakrebs (CRPC) im Frühstadium aufweist.

11. Abirateronacetat zur Verwendung nach einem der Ansprüche 8 bis 10, wobei der menschliche Patient mit kastrationsresistentem Prostatakrebs (CRPC) keine zytotoxische Chemotherapie erhalten hat.

Revendications

1. Procédé de prédiction d'une probabilité de survie après traitement avec l'acétate d'abiratérone (AA) chez un patient humain ayant un cancer de la prostate résistant à la castration (CPRC), le procédé comprenant :

(a) la mise en contact d'ADNc d'un échantillon de tumeur du patient obtenu avant traitement avec l'acétate d'abiratérone (AA) avec une puce à ADN, dans lequel ladite puce à ADN comprend des sondes pour au moins un biomarqueur d'ARNm, et dans lequel l'au moins un biomarqueur d'ARNm comprend le membre C3 de la famille de l'aldo-céto-réductase 1 (AKR1C3), la protéine de liaison 5 de FK506 (FKBP5) et l'antigène nucléaire de prolifération cellulaire (PCNA) ;
(b) la mesure d'un taux d'expression de l'au moins un biomarqueur d'ARNm ; et
(c) la comparaison du taux d'expression de l'au moins un biomarqueur d'ARNm à un taux d'expression d'un gène de référence, dans lequel une augmentation du taux d'expression du membre C3 de la famille de l'aldo-céto-réductase 1 (AKR1C3), de la protéine de liaison 5 de FK506 (FKBP5) ou de l'antigène nucléaire de prolifération cellulaire (PCNA), ou une combinaison quelconque de ceux-ci dans l'échantillon du patient par rapport au taux d'expression du gène de référence indique une probabilité accrue de survie sans progression, de survie globale, ou des deux pour ledit patient après traitement avec l'acétate d'abiratérone (AA).

2. Procédé de prédiction d'une probabilité de survie après traitement avec l'acétate d'abiratérone (AA) chez un patient humain ayant un cancer de la prostate résistant à la castration (CPRC), le procédé comprenant :

(a) l'isolement d'ARN à partir d'un échantillon de tumeur dudit patient ;
(b) la synthèse d'ADNc à partir de l'ARN ;
(c) la mesure d'un taux d'expression d'au moins un biomarqueur d'ARNm à partir de l'échantillon de tumeur, dans lequel l'au moins un biomarqueur d'ARNm comprend le membre C3 de la famille de l'aldo-céto-réductase 1 (AKR1C3), la protéine de liaison 5 de FK506 (FKBP5) ou l'antigène nucléaire de prolifération cellulaire (PCNA) ou une combinaison quelconque de ceux-ci, et dans lequel le taux d'expression est mesuré par RT-PCR quantitative ; et
(d) la détermination de l'expression relative de l'au moins un biomarqueur d'ARNm par rapport à l'expression d'un gène de référence, dans lequel une augmentation du taux d'expression du membre C3 de la famille de l'aldo-céto-réductase 1 (AKR1C3), de la protéine de liaison 5 de FK506 (FKBP5) ou de l'antigène nucléaire de prolifération cellulaire (PCNA) ou une combinaison quelconque de ceux-ci dans l'échantillon du patient par rapport au taux d'expression du gène de référence indique une probabilité accrue de survie sans progression, de survie globale, ou des deux pour ledit patient après traitement avec l'acétate d'abiratérone (AA).

3. Procédé selon l'une quelconque des revendications précédentes, dans lequel le taux d'expression de l'au moins un biomarqueur d'ARNm est augmenté par rapport à la valeur d'expression médiane de l'au moins un biomarqueur d'ARNm d'une population de patients.

4. Procédé selon l'une quelconque des revendications précédentes, dans lequel le patient humain a un cancer de la prostate résistant à la castration (CPRC) non métastatique ou à un stade précoce.

5. Procédé selon l'une quelconque des revendications 2 à 4, dans lequel le patient humain ayant un cancer de la prostate résistant à la castration (CPRC) n'a pas reçu une chimiothérapie cytotoxique.

6. Procédé selon l'une quelconque des revendications précédentes, le procédé comprenant en outre une étape de sélection dudit patient pour traitement avec une quantité thérapeutiquement efficace d'acétate d'abiratérone (AA) et de prednisone pour traiter ledit patient.

7. Acétate d'abiratérone (AA) pour utilisation dans un procédé de traitement du cancer de la prostate résistant à la castration (CPRC), le procédé comprenant la prédiction d'une probabilité de survie après traitement avec l'acétate d'abiratérone (AA) chez un patient humain par :

(a) mise en contact d'ADNc provenant d'un échantillon de tumeur du patient obtenu avant traitement avec

l'acétate d'abiratérone (AA) avec une puce à ADN, ladite puce à ADN comprenant des sondes pour au moins un biomarqueur d'ARNm, et l'au moins un biomarqueur d'ARNm comprenant le membre C3 de la famille de l'aldo-céto-réductase 1 (AKR1C3), la protéine de liaison 5 de FK506 (FKBP5) et l'antigène nucléaire de prolifération cellulaire (PCNA) ;
(b) mesure d'un taux d'expression de l'au moins un biomarqueur d'ARNm ;
(c) comparaison du taux d'expression de l'au moins un biomarqueur d'ARNm à un taux d'expression d'un gène de référence, une augmentation du taux d'expression du membre C3 de la famille de l'aldo-céto-réductase 1 (AKR1C3), de la protéine de liaison 5 de FK506 (FKBP5) ou de l'antigène nucléaire de prolifération cellulaire (PCNA), ou une combinaison quelconque de ceux-ci dans l'échantillon du patient par rapport au taux d'expression du gène de référence indiquant une probabilité accrue de survie sans progression, de survie globale, ou des deux pour ledit patient après traitement avec l'acétate d'abiratérone (AA) ; et
(d) si ledit patient a une probabilité accrue de survie sans progression, de survie globale, ou des deux pour ledit patient après traitement avec l'acétate d'abiratérone (AA) selon l'étape (c), traitement dudit patient avec une quantité thérapeutiquement efficace d'acétate d'abiratérone (AA) et de prednisone.

8. Acétate d'abiratérone (AA) pour utilisation dans un procédé de traitement d'un cancer de la prostate résistant à la castration (CPRC), le procédé comprenant la prédiction d'une probabilité de survie après traitement avec l'acétate d'abiratérone (AA) chez un patient humain par :

(a) isolement d'ARN à partir d'un échantillon de tumeur dudit patient ;
(b) synthèse d'ADNc à partir de l'ARN ;
(c) mesure d'un taux d'expression d'au moins un biomarqueur d'ARNm à partir de l'échantillon de tumeur, l'au moins un biomarqueur d'ARNm comprenant le membre C3 de la famille de l'aldo-céto-réductase 1 (AKR1C3), la protéine de liaison 5 de FK506 (FKBP5) ou l'antigène nucléaire de prolifération cellulaire (PCNA) ou une combinaison quelconque de ceux-ci, et le taux d'expression étant mesuré par RT-PCR quantitative ;
(d) détermination de l'expression relative de l'au moins un biomarqueur d'ARNm par rapport à l'expression d'un gène de référence, une augmentation du taux d'expression du membre C3 de la famille de l'aldo-céto-réductase 1 (AKR1C3), de la protéine de liaison 5 de FK506 (FKBP5) ou de l'antigène nucléaire de prolifération cellulaire (PCNA) ou une combinaison quelconque de ceux-ci dans l'échantillon du patient par rapport au taux d'expression du gène de référence indiquant une probabilité accrue de survie sans progression, de survie globale, ou des deux pour ledit patient après traitement avec l'acétate d'abiratérone (AA) ; et
(e) si ledit patient a une probabilité accrue de survie sans progression, de survie globale, ou des deux pour ledit patient après traitement avec l'acétate d'abiratérone (AA) selon l'étape (d), traitement dudit patient avec une quantité thérapeutiquement efficace d'acétate d'abiratérone (AA) et de prednisone.

9. Acétate d'abiratérone pour utilisation selon l'une quelconque des revendications 7 ou 8, le taux d'expression de l'au moins un biomarqueur d'ARNm étant augmenté par rapport à la valeur d'expression médiane de l'au moins un biomarqueur d'ARNm d'une population de patients.

10. Acétate d'abiratérone pour utilisation selon l'une quelconque des revendications 7 à 9, le patient humain ayant un cancer de la prostate résistant à la castration (CPRC) non métastatique ou à un stade précoce.

11. Acétate d'abiratérone pour utilisation selon l'une quelconque des revendications 8 à 10, le patient humain ayant un cancer de la prostate résistant à la castration (CPRC) n'ayant pas reçu une chimiothérapie cytotoxique.

REFERENCES CITED IN THE DESCRIPTION

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