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(54) **Title**: USE OF AN EFFICACY MARKER FOR OPTIMIZING THERAPEUTIC EFFICACY OF AN ANTI-HUMAN PD-1 ANTIBODY ON CANCERS

(57) **Abstract**: A purpose of the present invention is to provide a method capable of more effectively prescribing an anti-human PD-1 antibody for anti-cancer therapy, a method for estimating or optimizing therapeutic efficacy thereof, and further an efficacy marker that can be used in methods thereof. The present invention enables selection of the cancer patient in whom the therapeutic efficacy of the anti-human PD-1 antibody can be expected in future, by measuring the change which is more than a certain level of several kinds of efficacy markers in blood after administering the initial dose or doses of the anti-human PD-1 antibody compared to that prior to administering the initial dose, and provides a new prescription of the anti-human PD-1 antibody for anti-cancer therapy.

Description

Title of Invention: USE OF AN EFFICACY MARKER FOR OPTIMIZING THERAPEUTIC EFFICACY OF AN ANTI-HUMAN PD-1 ANTIBODY ON CANCERS

Technical Field

[0001] The present invention relates to use of an efficacy marker for estimating or optimizing therapeutic efficacy of an anti-human PD-1 antibody for a particular cancer patient.

Background Art

[0002] Currently, the first standard therapy for the permanent cure for cancer is chemical therapy, hormone therapy, or irradiation therapy, or combination thereof, but there has been a problem of occurrence of the side-effects. On the other hand, immune therapy has attracted attention as a promising therapy that avoids the side effects of traditional therapies. However, a characteristic of the immune therapy is mechanisms of action via cancer immunity of a patient, and therefore a large part of the therapy is yet unclear, its effects are different among individuals, and it is said that a relatively long term is required for treatment. In particular, in the case of a new medical agent that may require a relatively long period of treatment, it is very difficult to determine timing for evaluation of effectiveness for each of the patients, and in the case of adopting conventional timing to evaluate, even if the therapy can actually generate anti-tumor effects, its evaluation would be determined as no effect before confirming the effect. Therefore, in order to overcome the problem for the immune therapy, a method for detecting a pharmacological reaction before the timing to judge the effect, namely, a determination method capable of estimating the treatment effect has been required.

[0003] The anti-human PD-1 antibody is utilized as an anticancer and as an agent for fighting infections diseases. It acts as an agent for enhancing cancer immunity by suppressing the immune suppression signal via PD-1, which is an immune suppression receptor (See WO 06/121168, WO 03/011911, and WO 04/004771, incorporated herein by reference in their entirety.). However, a determination method capable of estimating the therapeutic effects has not been reported yet.

[0004] The present invention provides compositions and methods for detecting the efficacy of anti-human PD-1 antibody therapies and includes immunoglobulin(s), CD5L, gelsolin, and the like, which change in the blood, as biomarkers capable of estimating the therapeutic effects by the anti-human PD-1 antibody. For the immunoglobulins, in Nishimura et al., (and three persons), International Immunology, Vol. 10, No. 10, 1998, p. 1563-1572, it has been reported that the increase of serum IgG_3, IgG_{2b}, and

IgA of the PD-1 deficient mouse is observed, and for gelsolin, in Yang et al., (and nine persons), BMC Cancer, Vol. 6, No. 203, 2006, p. 1-10, the relationship between expression amount of gelsolin and death risk has been reported, but the relationship between the gelsolin expression level and the anti-cancer effects by the anti-human PD-1 antibody has not been reported at all.

Summary of Invention

[0005] A purpose of the present invention is to provide a method for more effectively prescribing an anti-human PD-1 antibody for a particular cancer patient, a method for estimating or optimizing therapeutic efficacy thereof, and further the efficacy marker that can be used in methods thereof.

[0006] The present invention provides efficacy markers in blood that change prior to the therapeutic effects of an anti-human PD-1 antibody.

[0007] In preferred embodiments, the present invention provides.

[0008] [1] A method for optimizing therapeutic efficacy of an anti-human PD-1 antibody on cancer, comprising subsequently administering one or more doses of an anti-human PD-1 antibody in the cancer patient in whom concentrations of one or more efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

[2] The method of [1], wherein the concentrations of the efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody are those at any timing before the twelfth week after administering the initial dose.

[3] The method of [1], wherein the concentrations of the efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody are those at any timing before the eighth week after administering the initial dose.

[4] The method of [1], wherein the immunoglobulin(s) is/are one or more isotypes selected from the group consisting of IgM, IgG and IgA.

[5] The method of [4], wherein IgG is IgG_4.

[6] The method of [1], wherein the anti-human PD-1 antibody is a human anti-human PD-1 antibody.

[7] The method of [6], wherein the human anti-human PD-1 antibody is the antibody specified as 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, or 2D3 described in WO 06/121168.

[8] The method of [1], wherein the cancer patient is a patient having one or more kinds of solid cancers.

[9] The method of [8], wherein one or more kinds of solid cancers is/are selected from the group consisting of malignant melanoma, kidney cancer, prostate cancer,

breast cancer, lung cancer, pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer, and urothelial cancer.

[10] Use of one or more efficacy markers for optimizing therapeutic efficacy of an anti-human PD-1 antibody on cancer, wherein the optimization comprises subsequently administering one or more doses of the anti-human PD-1 antibody in the cancer patient in whom concentrations of one or more efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

[0009] [11] The use of [10], wherein the concentrations of the efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody are those at any timing before the twelfth week after administering the initial dose.

[12] The use of [10], wherein the concentrations of the efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody are those at any timing before the eighth week after administering the initial dose.

[13] The use of [10], wherein the immunoglobulin(s) is/are one or more isotypes selected from the group consisting of IgM, IgG and IgA.

[14] The use of [13], wherein IgG is IgG_4.

[15] The use of [10], wherein the anti-human PD-1 antibody is a human anti-human PD-1 antibody.

[16] The use of [15], wherein the human anti-human PD-1 antibody is the antibody specified as 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, or 2D3 described in WO 06/121168.

[17] The use of [10], wherein the cancer patient is a patient having one or more kinds of solid cancers.

[18] The use of [17], wherein one or more kinds of solid cancers is/are selected from the group consisting of malignant melanoma, kidney cancer, prostate cancer, breast cancer, lung cancer, pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer and urothelial cancer.

[19] A method of treating for cancer, comprising subsequently administering one or more doses of an anti-human PD-1 antibody in the cancer patient in whom concentrations of one or more efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

[20] The method of [19], wherein the concentrations of the efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody are those

at any timing before the twelfth week after administering the initial dose.

[0010] [21] The method of [19], wherein the concentrations of the efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody are those at any timing before the eighth week after administering the initial dose.

[22] The method of [19], wherein the immunoglobulin(s) is/are one or more isotypes selected from the group consisting of IgM, IgG and IgA.

[23] The method of [22], wherein IgG is IgG_4.

[24] The method of [19], wherein the anti-human PD-1 antibody is a human anti-human PD-1 antibody.

[25] The method of [24], wherein the human anti-human PD-1 antibody is the antibody specified as 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, or 2D3 described in WO 06/121168.

[26] The method of [19], wherein the cancer patient is a patient having one or more kinds of solid cancers.

[27] The method of [26], wherein one or more kinds of solid cancers is/are selected from the group consisting of malignant melanoma, kidney cancer, prostate cancer, breast cancer, lung cancer, pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer, and urothelial cancer.

[28] An anticancer agent comprising an anti-human PD-1 antibody for treating the cancer patient in whom concentrations of one or more efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

[29] The anticancer agent of [28], wherein the concentrations of the efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody are those at any timing before the twelfth week after administering the initial dose.

[30] The anticancer agent of [28], wherein the concentrations of the efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody are those at any timing before the eighth week after administering the initial dose.

[0011] [31] The anticancer agent of [28], wherein the immunoglobulin(s) is/are one or more isotypes selected from the group consisting of IgM, IgG and IgA.

[32] The anticancer agent of [31], wherein IgG is IgG_4.

[33] The anticancer agent of [28], wherein the anti-human PD-1 antibody is a human anti-human PD-1 antibody.

[34] The anticancer agent of [33], wherein the human anti-human PD-1 antibody is the antibody specified as 17D8, 4H1, 5C4, 4A11, 7D3, 5F4 or 2D3 described in WO 06/121168.

[35] The anticancer agent of [28], wherein the cancer patient is a patient having one or more kinds of solid cancers.

[36] The anticancer agent of [35], wherein one or more kinds of solid cancers is/are selected from the group consisting of malignant melanoma, kidney cancer, prostate cancer, breast cancer, lung cancer, pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer and urothelial cancer.

[37] A method for estimating therapeutic efficacy of an anti-human PD-1 antibody on cancer, comprising comparing the concentrations of one or more efficacy markers in cancer patient's blood after administering an initial dose or doses of the anti-human PD-1 antibody with those prior to administering the initial dose and estimating that the anti-human PD-1 antibody is effective on treatment for cancers, based on significant increase of the concentrations of one or more efficacy markers after administering an initial dose or doses compared to those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from immunoglobulin(s), CD5L, gelsolin and fragments thereof.

[38] The method of [37], wherein the therapeutic efficacy is estimated based on significant increase of the concentrations of one or more efficacy markers in blood at any timing before the twelfth week after administering the initial dose compared to those prior to administering the initial dose.

[39] The method of [37], wherein the therapeutic efficacy is estimated based on significant increase of the concentrations of one or more efficacy markers in blood at any timing before the eighth week after administering the initial dose compared to those prior to administering the initial dose.

[40] The method of [37], wherein the immunoglobulin(s) is/are one or more isotypes selected from the group consisting of IgM, IgG and IgA.

[0012] [41] The method of [40], wherein IgG is IgG_4.

[42] The method of [37], wherein the cancer patient is a patient having one or more kinds of solid cancers.

[43] The method of [42], wherein the solid cancer(s) is/are one or more kinds selected from the group consisting of malignant melanoma, kidney cancer, prostate cancer, breast cancer, lung cancer, pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer and urothelial cancer.

[44] The method of [37], wherein the anti-human PD-1 antibody is a human anti-human PD-1 antibody.

[45] The method of [44], wherein the anti-human PD-1 antibody is the human antibody specified as 17D8, 4H1, 5C4, 4A11, 7D3, 5F4 or 2D3 described in WO

06/121168.

[46] A method for selecting the patient suitable for the treatment for cancer with an anti-human PD-1 antibody, comprising selecting the patient in whom concentrations of one or more efficacy markers in blood after administering an initial dose or doses of an anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

[0013] The present invention provides a new prescription method of the anti-human PD-1 antibody for anti-cancer therapy that is proceeded to administer to the cancer patient in whom its effect can be expected in future and that is not administered or is early stopped being administered to a patient in whom its effect cannot be expected.

Brief Description of Drawings

[0014] [fig.1]Figure 1 shows an effect of administration of the anti-mPD-1 antibody 4H2 on tumor volume.

[fig.2]Figure 2 shows increase of concentration of serum IgM in the administration group of the anti-mPD-1 antibody 4H2 and in the administration group of control mIgG.

[fig.3]Figure 3 shows increase of concentration of serum CD5L in the administration group of the anti-mPD-1 antibody 4H2 and in the administration group of control mIgG.

[fig.4]Figure 4 shows the relationship between increase of serum IgM concentration and tumor volume of each example in the administration group of the anti-mPD-1 antibody 4H2.

[fig.5]Figure 5 shows increase of concentration of serum IgG_4 in cancer patients who experienced a confirmed partial response or a stable disease by administration of the human anti-human PD-1 antibody.

Best Mode for Carrying out the Invention

[0015] Hereinafter, the present invention will be explained in detail.

[0016] In the present invention, human PD-1 is a protein specified by JP 07-291996.

[0017] In the present invention, the anti-human PD-1 antibody is, for example, a humanized anti-human PD-1 antibody or a human anti-human PD-1 antibody that is so-called a human PD-1 antagonist antibody or a human PD-1 neutralizing antibody capable of inhibiting immune suppression signal of human PD-1 wherein the humanized anti-human PD-1 antibody represents the antibody in which CDR (Complementarity Determining Region) sequence of an anti-human PD-1 antibody derived from another mammal such as a mouse is transplanted onto a framework sequence of a human antibody, and includes antibodies described in, for example, WO 06/021955.

[0018] Moreover, the human anti-human PD-1 antibody is the anti-human PD-1 antibody of which all of the structures such as CDR and the framework are derived from human, and includes antibodies described in, for example, WO 04/056875 and WO 06/121168, preferably is a human anti-human PD-1 antibody specified as 17D8(having V_H and V_L sequences as shown in SEQ ID NOs: 1 and 8, respectively), 4H1(having V_H and V_L sequences as shown in SEQ ID NOs: 3 and 10, respectively), 5C4(having V_H and V_L sequences as shown in SEQ ID NOs: 4 and 11, respectively), 4A11(having V_H and V_L sequences as shown in SEQ ID NOs: 5 and 12, respectively), 7D3(having V_H and V_L sequences as shown in SEQ ID NOs: 6 and 13, respectively), 5F4(having V_H and V_L sequences as shown in SEQ ID NOs: 7 and 14, respectively) or 2D3(having V_H and V_L sequences as shown in SEQ ID NOs: 2 and 9, respectively) described in WO 06/121168.

[0019] The above anti-human PD-1 antibodies can be produced based on methods described in the respective disclosed publications. Moreover, in the present invention, the anti-human PD-1 antibody includes an antibody fragment such as Fab, $F(ab)'_2$, ScFv of the above antibodies, and a low-molecular antibody such as $Sc(Fv)_2$ or diabody.

[0020] In the present invention, as an efficacy marker, namely, a marker capable of evaluating the therapeutic efficacy of the anti-human PD-1 antibody on cancer is a biological molecule or a fragment thereof of which the significant concentration change in cancer patent's blood prior to administering the initial dose and after administering the initial dose or doses of the anti-human PD-1 antibody in the cancer patient can be detected. For example, molecules of which the concentration increases include any one or more molecules selected from the group consisting of immunoglobulin(s), CD5L (CD5-like), gelsolin, complement C3, apolipoprotein, hemoglobin beta chain, mannose binding lectin, serpin A6, homeobox A10, EDEL3 (EGF-like repeats and discoidin I-like domains-containing protein 3), fibronectin 1, inter-alpha trypsin inhibitor 1, complement C4-B, C4b-binding protein, Ig kappa chain VIII region, immunoglobulin gamma 1 chain C region, angiotensinogen, alpha-1-antitrypsin-1, albumin, clotting factor XIII, kindlin 3, prothrombin, serine protease inhibitor A3K, Alpha-1 macroglobulin, plasminogen, complement B factor, murinoglobulin-1, murinoglobulin-4, integrin alpha 5 and fragments thereof, and are preferably any one or more molecules selected from the group consisting of the immunoglobulin(s), CD5L, gelsolin and fragments thereof, more preferably any one or more molecules selected from the group consisting of the immunoglobulin(s), CD5L and fragments thereof, and further preferably the immunoglobulin(s) or fragment(s) thereof. On the other hand, molecules of which the concentration decreases include any one or more molecules selected from the group consisting of haptoglobin, serum amyloid P component, serum amyloid A1, serum amyloid A2, serotransferrin, complement component factor H,

Complement C9, Inter-alpha trypsin inhibitor, hemopexin, thrombospondin-1 and fragments thereof. Here, the fragment of the molecule means one part of the biological molecule degraded by pretreatment for the measurement (for example, degradation by digestive enzyme such as trypsin) or by serum enzyme or the like.

[0021] In the present invention, the immunoglobulins include all of isotypes of, for example, IgM, IgG (such as IgG_1, IgG_2, IgG_3 or IgG_4), IgA (such as IgA_1 or IgA_2), IgD and IgE, preferably IgM, IgA or IgG, more preferably IgM or IgG_4. Moreover, the immunoglobulin concentration in blood means concentration of each isotype.

[0022] In the present invention, the respective efficacy marker is a protein specified by GenBank accession numbers in the following tables 1 to 3. In the tables, when there are many of accession numbers for one marker, it is indicated that the marker is specified by any one of the numbers. Moreover, the marker to which the sign "*" is appended is specified by the mentioned accession number as a mouse protein, and the marker to which the sign "**" is appended is specified by the mentioned accession number as a rat protein.

[0023] [Table 1]

Markers	GenBank Acc. Num.
CD5L	NP_005885.1
Gelsolin	NP_000168.1
C3 complement	NP_000055.2
Apolipoprotein	NP_000030.1
Hemoglobin beta chain	NP_000509.1
Mannose-binding lectin	NP_000233.1
Serpin A6	NP_001747.2

[0024]

[Table 2]

Markers	GenBank Acc. Num.
Homeobox A10	NP_061824.3 NP_714926.1
EDEL3	NP_005702.3
fibronectin 1	NP_002017.1 NP_473375.2 NP_997639.1 NP_997640.1 NP_997641.1 NP_997643.1 NP_997647.1
Inter-alpha-trypsin inhibitor 1	NP_002206.2
C4B complement	NP_001002029.3
C4B complement binding protein	NP_000706.1 NP_000707.1 NP_001017364.1 NP_001017365.1 NP_001017366.1 NP_001017367.1
Immunoglobulin kappa chain VIII region	S16833 S40381
Immunoglobulin gamma 1 chain C region	NP_064455.1 NP_690594.1
Angiotensinogen	NP_000020.1
Apha 1 antitrypsin 1	NP_000286.3 NP_001002235.1 NP_001002236.1 NP_001121172.1 NP_001121173.1 NP_001121174.1 NP_001121175. NP_001121176.1 NP_001121177.1 NP_001121178.1 NP_001121179.1
Albumin	NP_000468.1
Coagulation factor XIII	NP_001985
KINDLIN3	NP_113659.3 NP_848537.1
SPA3K*	NP_035588.1
Prothrombin	NP_000497.1
Alpha-1 Macroglobulin	NP_001624.1
Plasminogen	NP_000292.1
Complement factor B	NP_001701.2
Murinoglobulin-1*	NP_032671.2
Murinoglobulin-4**	XR_035729.1
Integrin alpha 5	NP_002196.2

[0025] [Table 3]

Markers	GenBank Acc. Num.
Haptoglobin	NP_001119574.1 NP_005134.1
Amyloid P Component	NP_001630.1
Serum Amyloid A1	NP_000322.2 NP_954630.1
Serum Amyloid A2	NP_001120852.1 NP_110381.2
Serotransferrin	NP_001054.1
Complement factor H	NP_000177.2 NP_001014975.1
C9 complement	NP_001728.1
Inter-alpha-trypsin inhibitor	NP_002208.3
Hemopexin	NP_000604.1
Thrombospondin-1	NP_003237.2

[0026] In the present invention, the timing prior to the administration of the anti-human PD-1 antibody can be any timing prior to administering the initial dose, but the timing immediately prior to administering the initial dose is preferable. On the other hand, the timing after administering the initial dose or doses of the anti-human PD-1 antibody can be any timing prior to confirming the anticancer effects of the anti-human PD-1 antibody by conventional measurement or a conventional evaluation method, but is more preferably any timing prior to approximately the twelfth week (more preferably, the eighth week) after administering the initial dose of the anti-human PD-1 antibody, further preferably the earliest timing in which a certain or more amount of change in the efficacy marker concentration in blood after the administration is observed and which is prior to approximately the eighth week after administering the initial dose. Moreover, the blood sampling and the measurement of the efficacy marker concentration after administering the initial dose or doses are not limited to one time, but are preferably performed at a plurality of times (for example, two to twelve times or more).

[0027] A dosage of the anti-human PD-1 antibody varies depending on age, weight, symptom (such as cancer), treatment effect, administration method, treatment time and the like, but the administration is performed, for example, in the range of about 1 to 30 mg/kg at one time, at one time every two to four weeks, for twelve weeks (at 3 to 6 times). Of course, as described above, the dosage varies depending on various conditions, and therefore a less dosage than the above range may be sufficient, or the dosage over the above range may be required to be administered.

[0028] For the patient in whom significant change in the efficacy marker concentration in blood is not observed by the administration of the anti-human PD-1 antibody, until at

least the significant change can be observed, a modified prescription such as increase in the dosage in the range of about 1 to 30 mg/kg, extension of dosing period, increase in the number of doses, or shortening of the dosing intervals may be performed.

[0029] In the present invention, the therapeutic efficacy on cancer may be evaluated based on Response Evaluation Criteria In Solid Tumors (hereinafter, abbreviated as RECIST) (Journal of the National Cancer Institute, 2000, Vol. 92, No. 3, 205-216), namely Complete Response (hereinafter abbreviated to CR) in which disappearance of all target lesions continues for four weeks or more, Partial Response (hereinafter abbreviated to PR) in which 30% or more decrease in the sum of the longest diameters of target lesions continues for four weeks or more, Progressive Disease (hereinafter abbreviated to PD) in which the sum of the longest diameters of target lesions increases by 20 % or more, compared with the smallest sum of the longest diameters recorded after the initiation of the treatment, and Stable Disease (hereinafter abbreviated as SD) in which shrinkage of tumor is insufficient for PR and increase of tumor, compared with the smallest sum of the longest diameters after the initiation of the treatment is insufficient for PD.

[0030] In the present invention, the significant increase of concentration of the efficacy marker in cancer patient's blood after administering the initial dose or doses of the anti-human PD-1 antibody over that prior to administering the initial dose means that the concentration of the efficacy marker after administering the initial dose or doses is more than the lower point of blood concentration range of the efficacy marker in the patient group evaluated as SD in RECIST, and may also mean that increase of blood concentration after administering the initial dose or doses over that prior to administering the initial dose is more than the lower point of range of said increase in the SD patient group. Further, when at least one kind of many efficacy markers meets the requirement above, said increase can be significant. And, blood concentration range of or said increase in each efficacy marker in each classification (CR, PR, SD, PD), particularly SD, can be calculated by statistical analysis of blood concentration or said increase in blood concentration over that prior to administering the initial dose in the patients evaluated as SD from many of cancer patients in which the anti-human PD-1 antibody is administered in advance.

[0031] The present invention includes the method for estimating the therapeutic efficacy of the anti-human PD-1 antibody on cancers comprising;

(1) measuring concentrations of one or more efficacy markers above in cancer patient's blood prior to administering the initial dose of the anti-human PD-1 antibody and those after administering the initial dose or doses, respectively;

(2) comparing both concentrations of one or more efficacy markers; and

(3) estimating that the anti-human PD-1 antibody is effective on treatment for

cancers, based on the significant increase of the concentrations of one or more efficacy markers after administering the initial dose or doses compared to those prior to administering the initial dose.

[0032] Further, the present invention includes the method for optimizing the therapeutic efficacy of the anti-human PD-1 antibody on cancers, comprising:

(1) measuring concentrations of one or more efficacy markers above in cancer patient's blood prior to administering the initial dose of the anti-human PD-1 antibody and those after administering the initial dose or doses, respectively;

(2) comparing both concentrations of one or more efficacy markers; and

(3) subsequently administering one or more doses of the anti-human PD-1 antibody in the cancer patient in whom the concentrations of one or more efficacy markers in blood after administering the initial dose or doses of the anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose.

[0033] Likewise, the present invention includes the use of one or more efficacy markers above for optimization of the therapeutic efficacy of an anti-human PD-1 antibody on cancers, wherein the optimization comprises;

(1) measuring concentrations of one or more efficacy markers above in cancer patient's blood prior to administering the initial dose of the anti-human PD-1 antibody and those after administering the initial dose or doses, respectively

(2) comparing both concentrations of one or more efficacy markers; and

(3) subsequently administering one or more doses of the anti-human PD-1 antibody in the cancer patient in whom the concentrations of one or more efficacy markers in blood after administering the initial dose or doses of the anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose.

[0034] Further, the present invention includes the method of treating for cancer, comprising subsequently administering one or more doses of an anti-human PD-1 antibody in the cancer patient in whom concentrations of one or more efficacy markers above in blood after administering the initial dose or doses of the anti-human PD-1 antibody significantly increase more than those prior to administering the initial dose.

[0035] For measurement of concentrations of the efficacy markers, each cancer patient's blood before and after the administration of the anti-human PD-1 antibody is used. The method of blood sampling is not particularly limited, but to prevent blood clotting, an anticoagulant agent may be used. The anticoagulant agent includes heparin, sodium citrate, EDTA and the like. The blood may be separated into serum by a well-known method in the art or the method described in Examples and may be measured as it is or may be stored. When blood concentrations of many efficacy markers are measured, each efficacy marker may be measured individually, or all thereof may be measured cyclopaedically.

[0036] In the present invention, concentrations of the efficacy markers, particularly the immunoglobulin(s), CD5L, gelsolin or fragments thereof can be measured by a well-known method in the art, preferably an immunological method and a mass spectrometric method.

[0037] The immunological measurement can be conducted by a well-known method in the art or the method described in Examples, and includes, for example, enzyme immunoassay (EIA) (such as enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassay (CLIA) and electrochemiluminescence immunoassay (ECLIA)), radioimmune assay (RIA) (such as immuno radio metric assay (IRMA), radio receptor assay (RRA), radio assay (RA) and competitive protein binding assay (CPBA)), fluorescence antibody technique (FA) (such as fluoroimmunoassay (FIA), time-resolved fluoroimmunoassay (TR-FAI), indirect fluorescent antibody technique (IFA)), fluorescence polarization immunoassay (FPIA) (such as Evanescent wave fluoroimmunoassay (EV-FIA) and Fluorescence polarization assay (FPA)), immunoprecipitation technique, turbidimetrical immunoassay (TIA), particle counting immunoassay (PCIA) (such as latex agglutination (LA), particle mediated immunoassay (PAM-IA) and latex photometric immunoassay (LPIA)), nephelometry method, western blotting, immunostaining, immunodiffusion method and the like.

[0038] The mass spectrometric method can be conducted by a well-known method in the art, for example, supplying samples to the method of combining a sample-introducing part (such as gel electrophoresis pathway, liquid chromatography (such as ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, and reverse phase chromatography)), a ion source (such as electron ionization, chemical ionization, field desorption, high-speed atomic collision, matrix-assisted laser desorption/ ionization, electrospray ionization, and atmospherical pressure chemical ionization) and a mass spectrometer (double-focusing mass spectrometer, quadrupole mass spectrometer, time-of-flight mass spectrometer, and Fourier transform mass spectrometer, ion cyclotron mass spectrometer), and detecting bands, spots or peaks corresponding to the molecular mass of predefined marker peptides, and specifically includes liquid chromatography-mass spectrometry (LC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS).

[0039] In the present invention, in particular, when the efficacy marker is the immunoglobulin or fragments thereof, the measurement is preferably ELISA, turbidimetrical immunoassay, nephelometry or latex photometric immunoassay, and when the efficacy marker is CD5L or gelsolin or fragments thereof, the measurement is preferably ELISA or the mass spectrometric method (such as LC/MS or LC/MS/MS).

[0040] The cancer patient to whom the present invention can be applied is not particularly limited, but its effect can be more expected in the patient having solid cancer. Such

solid cancer includes, for example, malignant melanoma (melanoma (such as metastatic malignant melanoma)), kidney cancer (such as renal cell cancer, and clear cell carcinoma), prostate cancer (such as hormone refractory prostate adenocarcinoma), breast cancer, lung cancer (such as non-small-cell lung cancer), pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer, urothelial cancer, colonic cancer, bone cancer, skin cancer, head and neck cancer, skin or orbital malignant melanoma, uterus cancer, rectal cancer, anal cancer, testicle cancer, tubal carcinoma, endometrial carcinoma, uterus neck carcinoma, vaginal carcinoma, vulva carcinoma, small intestinal cancer, endocrine system cancer, thyroid cancer, parathyroid cancer, adrenal cancer, soft tissue sarcomas, urethral cancer, penis cancer, childhood solid cancer, bladder cancer, renal or ureter cancer, renal pelvic carcinoma, central nervous system (CNS) tumor, tumor new vascular channel formation, spine tumor, brain-stem glioma, pituitary adenoma, Kaposi's sarcoma, squamous cell cancer, carcinoma planocellulare and environment-induced cancer including asbestos-induced cancer and combinations of the cancers. The solid cancer for which the effect of the present invention can be more expected includes malignant melanoma (melanoma (such as metastatic malignant melanoma)), kidney cancer (such as renal cell cancer and clear cell carcinoma), prostate cancer (such as hormone refractory prostate adenocarcinoma), breast cancer, lung cancer (such as non-small-cell lung cancer), pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer, urothelial cancer and combination of the cancers. The solid cancer for which further effect of the present invention can be expected includes malignant melanoma (melanoma (such as metastatic malignant melanoma)), kidney cancer (such as renal cell cancer and clear cell carcinoma), prostate cancer, lung cancer (such as non-small-cell lung cancer), intestinal cancer, liver cell cancer, biliary tract cancer and combination of said cancers.

[0041] Moreover, the present invention can also be applied to chronic or acute leukemia including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia and chronic lymphocytic leukemia, lymphocytic lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, primary CNS lymphoma and T cell lymphoma, which are categorized to so-called blood cancers.

[0042] The anti-human PD-1 antibody used in the present invention can be produced by the method described in WO 06/121168.

[0043] The anti-human PD-1 antibody used in the present invention is generally administered systemically or locally in a parenteral form, for example, administered intravenously, intramuscularly, intradermally, intraperitoneally, or subcutaneously by injection or transfusion. Moreover, the anti-human PD-1 antibody used in the present

invention may be administered with other combind drug described in, for example, WO 06/121168.

Description of Embodiments

[0044] Hereinafter, the present invention will be explained in detail by Examples, but the present invention is not limited thereto.

Example 1

[0045] Preparation of MC38 Cells for Transplantation

[0046] In the day before transplantation, 5 x 10^6 cells/30 mL/150 mm culture dish of MC38 cells (mouse colon adenocarcinoma (Cancer Res. (1975), 35(9), p.2434-9)) was seeded on DMEM culture containing 10% fetal bovine serum (FBS), 100 U/mL of penicillin and 100 microgram/mL of streptomycin (hereinafter abbreviated as normal culture), and cultured for one day at 37 degrees Celsius under 5% CO_2/95% air.

[0047] In the day of transplantation, the culture supernatant was collected, and MC38 cells were washed with Dulbecco's phosphate buffer (D-PBS) and then collected by a normal method. The collected cells were suspended in D-PBS, and then stored on ice until just before transplantation.

Example 2

[0048] Measurement of Tumor Volume in Tumor-bearing Model of MC38 Cells

[0049] Into the right abdomen of mouse (7 weeks age, female C57BL/6NCr1Cr1j mouse (Japan Charies River Co., Ltd.); ten examples) under anesthesia, 2 x 10^5 cells/100 microliter/mouse of MC38 cells were subcutaneously administered. 600 microgram/200 microliter/mouse of the anti-mouse PD-1 antibody 4H2 (hereinafter, abbreviated as anti-mPD-1 antibody 4H2 or 4H2) and the mouse IgG (hereinafter abbreviated as mIgG) were intraperitoneally administered, respectively, at one hour before transplantation (day 0), and on day 3, day 6 and day 10 after transplantation.

[0050] The blood sampling from tail vein was performed the day before transplantation and on day 8 and day 15 after transplantation, and furthermore the blood was stood still for 3 hours at room temperature, and then separated into serum by centrifugation, and stored at -80 degrees Celsius. Furthermore, abdominal cavity of the mouse was opened under anesthesia on day 24 after transplantation, and the blood was drawn from the aorta abdominalis and stored, by the same method as described above.

[0051] The tumor volume (mm^3) was calculated by the following formula after measuring the minor axis and the major axis of the tumor by using an electronic caliper (Mitutoyo Corporation).

[0052] Tumor Volume (mm^3) = [(Minor Axis)^2 x (Major Axis)]/2

[0053] Figure 1 shows change of the tumor volumes in the control group of single administration of 600 microgram of mIgG (black square) and in the group of single admin-

istration of the same amount of anti-mPD-1 antibody (white triangle).

[0054] (Results)

[0055] As shown in figure 1, the anti-mPD-1 antibody 4H2 showed the effect of significantly reducing the tumor volume.

Example 3

[0056] Measurement of IgM Concentration and CD5L Concentration in the Serum

[0057] IgM concentration in serum was measured by ELISA Starter Accessory Package kit (Funakoshi Corporation) and mouse IgM ELISA Quantitation kit (Funakoshi Corporation) by following the operating procedure described in the package leaflet.

[0058] Measurement of CD5L concentration in serum was measured according to the following operating procedure. That is, 100 microliter/well of 1 microgram/mL of anti-mouse CD5L monoclonal antibody (MAB28341) in PBS dilute solution was dispensed to an ELISA plate and was stood still at 4 degrees Celsius overnight. The plate was washed three times with washing buffer (0.05% (v/v) Tween 20/PBS) (100 microliter/well), to which 100 microliter/well of blocking buffer (1% (w/v) BSA/PBS) was added, and then made to stand still at room temperature for 90 minutes.

[0059] Furthermore, the plate was washed three times with washing buffer (100 microliter/well), to which serially diluted 10 to 0.078 ng/mL of recombinant mouse CD5L (R&D systems) and 100 microliter/well of 10^3 times diluted serum sample were added, and then made to stand still at room temperature for 120 minutes.

[0060] The plate was washed three times with washing buffer, to which 100 microliter/well of 1 microgram/mL of anti-mouse CD5L polyclonal antibody (AF2834) was added, and then made to stand still at room temperature for 60 minutes.

[0061] Furthermore, the plate was washed three times with washing buffer, to which 100 microliter/well of 10^5 times diluted HRP-labelled anti-goat IgG was added, and then stood still at room temperature for 60 minutes. The plate was washed three times with washing buffer, to which 100 microliter/well of TMB substrate (KPL) was added, and then stood still at room temperature for 30 minutes. 100 microliter/well of stop solution (KPL) was added to the plate, and then absorption of light at 450 nm was measured by a spectrophotometer for microplate (SPECTRA MAX™ 190; molecular device).

[0062] Figures 2 and 3 show the increase of IgM concentration in serum and CD5L concentration in serum, respectively, in the group of administration of anti-mPD-1 antibody 4H2 on day 8 after transplantation of MC38 cells and in the control group of administration of mIgG. Here, the increase of each concentration represents the increase amount from each concentration in the day before transplantation (average of ten examples for each group).

[0063] Figure 4 shows the relationship between the increase of IgM concentration in serum

in the group of administration of anti-mPD-1 antibody 4H2 on day 8 after transplantation and the tumor volume on day 15 after transplantation.

[0064] (Results)

[0065] As shown in figures 2 and 3, in the group of administration of anti-mPD-1 antibody 4H2, on day 8 after transplantation in which the effect to the tumor volume could not be confirmed, the increase of IgM concentration in serum and the increase of CD5L concentration in serum were more significant than that of the group of administration of control mIgG ($P < 0.05$; Student's t-test). Moreover, as shown in figure 4, it was recognized that the increase of IgM concentration in serum in the group of administration anti-mPD-1 antibody 4H2 has an inverse relation (correlation coefficient: -0.58) with the tumor volume thereof. Similarly, CD5L also showed an inverse relation.

Example 4

[0066] 39 patients with recurrent or treatment-refractory solid tumors (including non-small cell lung cancer, renal, colon, melanoma and hormone-refractory prostate cancer) received single dose treatment of 0.3, 1, 3 or 10 mg/kg of the human anti-PD-1 antibody. The sera from patients were collected at 1 day before first dosing, and 29 days, 57 days and 85 days after first dosing. These sera were frozen until measurement of biomarker concentration. After thawing these sera, the concentration of the immunoglobulins (including IgM, IgA, IgG_1, IgG_2, IgG_3 and IgG_4) were measured.

[0067] (Result)

[0068] Disease status was evaluated by RECIST criteria. Anti tumor activity were observed, including two patients with colorectal cancer (received the treatments of the anti-human PD-1 antibody of 3 mg/kg) and renal cell cancer (received the treatments of the anti-human PD-1 antibody of 10 mg/kg), who experienced a confirmed partial response, and one patient with melanoma (received the treatments of the anti-human PD-1 antibody of 10 mg/kg), who experienced a stable disease. As shown in the figure 5, the concentrations of IgG_4 after administering the initial dose of the anti-human PD-1 antibody are higher than those prior to administering the initial dose.

Industrial Applicability

[0069] The anti-human PD-1 antibody used in the present invention can be continuously administered to the patient in whom its effect can be expected in future, and is useful as a new prescription of the anti-human PD-1 antibody as an active ingredient. Moreover, the method for estimating or optimizing the therapeutic efficacy of the anti-human PD-1 antibody used in the present invention on cancer is useful as means for providing the anti-human PD-1 antibody used in the present invention to the cancer patient in whom its effect can be expected.

Claims

[Claim 1] A method for optimizing therapeutic efficacy of an anti-human PD-1 antibody on cancer, comprising subsequently administering one or more doses of the anti-human PD-1 antibody in the cancer patient in whom concentrations of one or more efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

[Claim 2] The method of claim 1, wherein the concentrations of the efficacy markers in blood after administering the initial dose or doses of the anti-human PD-1 antibody are those at any timing before the twelfth week after administering the initial dose.

[Claim 3] The method of claim 1, wherein the concentrations of the efficacy markers in blood after administering the initial dose or doses of the anti-human PD-1 antibody are those at any timing before the eighth week after administering the initial dose.

[Claim 4] The method of claim 1, wherein the immunoglobulin(s) is/are one or more isotypes selected from the group consisting of IgM, IgG and IgA.

[Claim 5] The method of claim 4, wherein IgG is IgG_4.

[Claim 6] The method of claim 1, wherein the anti-human PD-1 antibody is a human anti-human PD-1 antibody.

[Claim 7] The method of claim 6, wherein the human anti-human PD-1 antibody is the antibody specified as 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, or 2D3 described in WO 06/121168.

[Claim 8] The method of claim 1, wherein the cancer patient is a patient having one or more kinds of solid cancers.

[Claim 9] The method of claim 8, wherein one or more kinds of solid cancers is/are selected from the group consisting of malignant melanoma, kidney cancer, prostate cancer, breast cancer, lung cancer, pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer, and urothelial cancer.

[Claim 10] Use of one or more efficacy markers for optimizing therapeutic efficacy of an anti-human PD-1 antibody on cancer, wherein the optimization comprises subsequently administering one or more doses of the anti-human PD-1 antibody in the cancer patient in whom concen-

trations of one or more efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

[Claim 11] The use of claim 10, wherein the concentrations of the efficacy markers in blood after administering the initial dose or doses of the anti-human PD-1 antibody are those at any timing before the twelfth week after administering the initial dose.

[Claim 12] The use of claim 10, wherein the concentrations of the efficacy markers in blood after administering the initial dose or doses of the anti-human PD-1 antibody are those at any timing before the eighth week after administering the initial dose.

[Claim 13] The use of claim 10, wherein the immunoglobulin(s) is/are one or more isotypes selected from the group consisting of IgM, IgG and IgA.

[Claim 14] The use of claim 13, wherein IgG is IgG_4.

[Claim 15] The use of claim 10, wherein the anti-human PD-1 antibody is a human anti-human PD-1 antibody.

[Claim 16] The use of claim 15, wherein the human anti-human PD-1 antibody is the antibody specified as 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, or 2D3 described in WO 06/121168.

[Claim 17] The use of claim 10, wherein the cancer patient is a patient having one or more kinds of solid cancers.

[Claim 18] The use of claim 17, wherein one or more kinds of solid cancers is/are selected from the group consisting of malignant melanoma, kidney cancer, prostate cancer, breast cancer, lung cancer, pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer and urothelial cancer.

[Claim 19] A method of treating for cancer, comprising subsequently administering one or more doses of an anti-human PD-1 antibody in the cancer patient in whom concentrations of one or more efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody significantly increased more than that prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

[Claim 20] The method of claim 19, wherein the concentrations of the efficacy

markers in blood after administering the initial dose of the anti-human PD-1 antibody are those at any timing before the twelfth week after administering the initial dose.

[Claim 21] The method of claim 19, wherein the concentrations of the efficacy markers in blood after administering the initial dose of the anti-human PD-1 antibody are those at any timing before the eighth week after administering the initial dose.

[Claim 22] The method of claim 19, wherein the immunoglobulin(s) is/are one or more isotypes selected from the group consisting of IgM, IgG and IgA.

[Claim 23] The method of claim 22, wherein IgG is IgG_4.

[Claim 24] The method of claim 19, wherein the anti-human PD-1 antibody is a human anti-human PD-1 antibody.

[Claim 25] The method of claim 24, wherein the human anti-human PD-1 antibody is the antibody specified as 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, or 2D3 described in WO 06/121168.

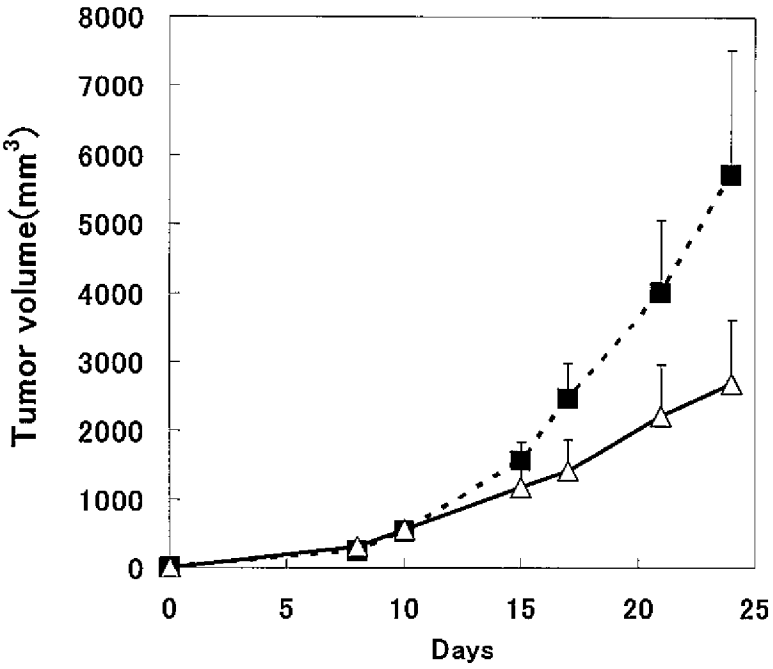
[Claim 26] The method of claim 19, wherein the cancer patient is a patient having one or more kinds of solid cancers.

[Claim 27] The method of claim 26, wherein one or more kinds of solid cancers is/are selected from the group consisting of malignant melanoma, kidney cancer, prostate cancer, breast cancer, lung cancer, pancreatic cancer, intestinal cancer, liver cell cancer, biliary tract cancer, stomach cancer, ovary cancer, esophageal cancer, and urothelial cancer.

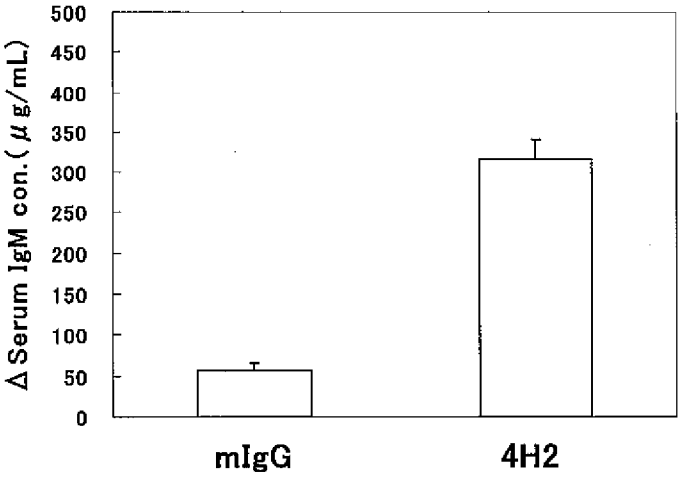
[Claim 28] An anticancer agent comprising an anti-human PD-1 antibody for treating the cancer patient in whom concentrations of one or more efficacy markers in blood after administering an initial dose or doses of the anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

[Claim 29] A method for selecting the patient suitable for the treatment for cancer with an anti-human PD-1 antibody, comprising selecting the patient in whom concentrations of one or more efficacy markers in cancer patient's blood after administering an initial dose or doses of an anti-human PD-1 antibody significantly increased more than those prior to administering the initial dose, wherein one or more efficacy markers is/are selected from the group consisting of immunoglobulin(s), CD5L, gelsolin, and fragments thereof.

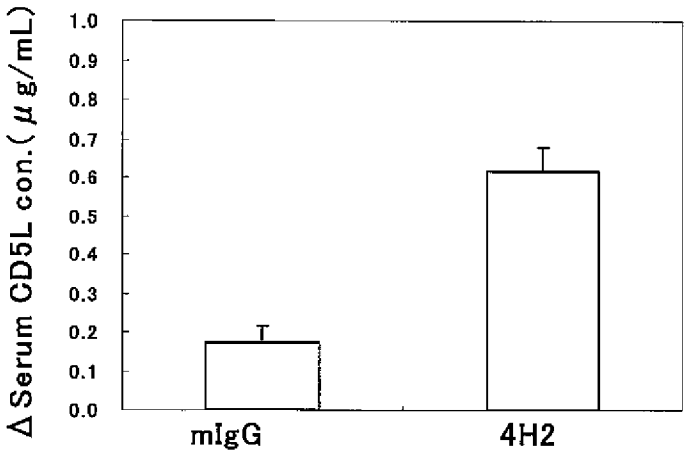
[Fig. 1]



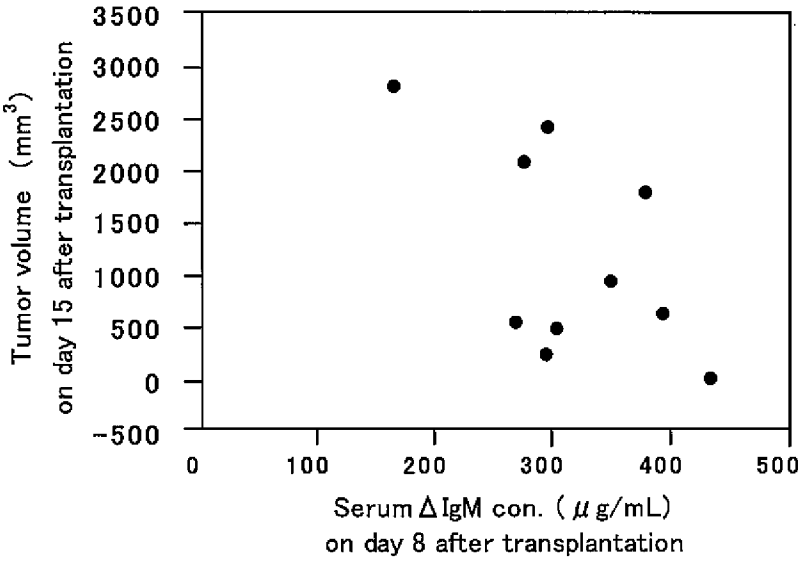
[Fig. 2]



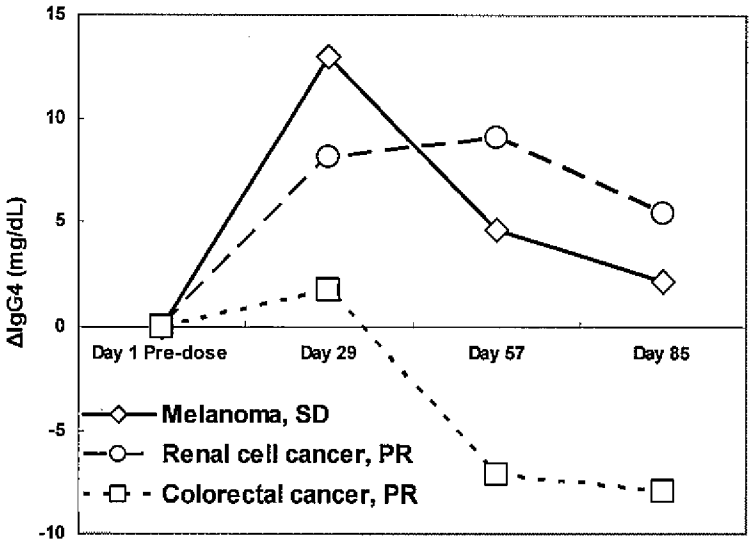
[Fig. 3]



[Fig. 4]


Tumor volume (mm3) on day 15 after transplantation
3500
3000
2500
2000
1500
1000
500
0
-500
0
100
200
300
400
500
Serum ΔIgM con. (μg/mL) on day 8 after transplantation

[Fig. 5]


ΔIgG4 (mg/dL)
15
10
5
0
-5
-10
Day 1 Pre-dose
Day 29
Day 57
Day 85
Melanoma, SD
Renal cell cancer, PR
Colorectal cancer, PR

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/003093

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. A61K39/395(2006.01)i, A61P35/00(2006.01)i, A61P35/02(2006.01)i, G01N33/53(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. A61K39/395, A61P35/00, A61P35/02, G01N33/53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2009
Registered utility model specifications of Japan 1996-2009
Published registered utility model applications of Japan 1994-2009

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

BIOSIS(STN), CAplus(STN), EMBASE(STN), MEDLINE(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2006-340714 A (ONO PHARMACEUTICAL CO., LTD.) 2006.12.21, Claims 1-105, Example 11 & EP 1896582 A & WO 2006/121168 A1	28
A	JP 7-291996 A (Tasuku Honjo) 1995.11.07, Claims 1-10 & US 5629204 A & EP 670369 A2	28

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19.08.2009	01.09.2009

Name and mailing address of the ISA/JP	Authorized officer
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4C 3229

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/003093

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: 1-27, 29
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matters of claim 1-27, 29 relate to methods for treatment of the human body by surgery, therapy, or diagnostic methods, practiced on the human body.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

专利名称(译)	功效标记物用于优化抗人pd-1抗体对癌症的治疗功效的用途		
公开(公告)号	EP2307050A1	公开(公告)日	2011-04-13
申请号	EP2009773195	申请日	2009-07-03
[标]申请(专利权)人(译)	小野药品工业株式会社 米德列斯公司		
申请(专利权)人(译)	ONO PHARMACEUTICAL CO.，LTD. Medarex公司，INC.		
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IPC分类号	A61K39/395 A61P35/00 A61P35/02 G01N33/53 C07K16/28		
CPC分类号	A61K2039/505 A61P35/00 A61P35/02 A61P37/04 C07K16/2818 G01N2800/52		
优先权	2008176110 2008-07-04 JP		
其他公开文献	EP2307050A4		
外部链接	Espacenet		

摘要(译)

本发明的目的是提供一种能够更有效地处方用于抗癌治疗的抗人PD-1抗体的方法，用于估计或优化其治疗功效的方法，以及可用于其方法。本发明通过测量给药后血液中几种功效标志物的一定水平以上的变化，能够选择未来可预期抗人PD-1抗体的治疗效果的癌症患者。与施用初始剂量之前相比，抗人PD-1抗体的初始剂量或剂量，并提供用于抗癌疗法的抗人PD-1抗体的新处方。