

Claims

[Claim 1]

A method of identifying a human subject having, suspected of having, or at risk of developing, a renal cell carcinoma in need of a combination therapy comprising lenvatinib or a pharmaceutically acceptable salt thereof and everolimus, the method comprising:

assaying a biological sample obtained from the human subject before administering the combination therapy comprising lenvatinib or a pharmaceutically acceptable salt thereof and everolimus and determining that the concentration of angiopoietin-2 (Ang2) protein in the biological sample is high, as compared to a control; and

identifying the human subject having a high concentration of Ang2 protein in the biological sample as in need of the combination therapy comprising lenvatinib or a pharmaceutically acceptable salt thereof and everolimus,

wherein the biological sample is selected from the group consisting of a blood sample, a serum sample, a plasma sample, a renal cell carcinoma archived tumor sample, and a renal cell carcinoma biopsy sample, and

wherein the control is a pre-established cut-off value.

[Claim 2]

The method of claim 1, wherein the biological sample is a serum sample.

[Claim 3]

The method of claim 1 or 2, wherein the renal cell carcinoma is an advanced renal cell carcinoma or a metastatic renal cell carcinoma.

[Claim 4]

The method of any one of claims 1 to 3, wherein the human subject having, suspected of having, or at risk of developing, a renal cell carcinoma has experienced at least one prior VEGF-targeted therapy.

[Claim 5]

The method of any one of claims 1 to 4, wherein the pre-established cut-off value is an Ang2 protein concentration that is determined based on receiver operating characteristic analysis predicting tumor response with a higher positive predictive value compared to no cut-off, and wherein a concentration of Ang2 protein equal to or below the pre-established cut-off value is a low concentration of Ang2 and a value higher than the pre-established cut-off value is a high concentration of Ang2.

[Claim 6]

The method of claim 5, wherein tumor response is an objective response rate, a clinical benefit rate or % of maximum tumor shrinkage of at least 30%.

[Claim 7]

The method of any one of claims 1 to 4, wherein the pre-established cut-off value is an Ang2 protein concentration that is determined based on predicting survival using simulation models to separate two groups divided by the cut-off, and wherein a concentration of Ang2 protein equal to or below the pre-established cut-off value is a low concentration of Ang2 and a value higher than the pre-established cut-off value is a high concentration of Ang2.

[Claim 8]

The method of claim 7, wherein survival is overall survival.

[Claim 9]

The method of any one of claims 1 to 4, wherein the pre-established cut-off value is an Ang2 protein concentration within the range from 3565 to 5650 pg/ml, and wherein a concentration of Ang2 protein equal to or below the pre-established cut-off value is a low concentration of Ang2 and a value higher than the pre-established cut-off value is a high concentration of Ang2.

[Claim 10]

The method of any one of claims 1 to 9, wherein the concentration of Ang2 protein is measured by an immunological method.

[Claim 11]

The method of claim 10, wherein the immunological method is selected from the group consisting of enzyme immunoassay, radioimmunoassay, chemiluminescent immunoassay, electrochemiluminescence immunoassay, latex turbidimetric immunoassay, latex photometric immunoassay, immuno-chromatographic assay, and western blotting.

[Claim 12]

The method of any one of claims 1 to 10, wherein the concentration of the protein is measured by enzyme immunoassay.

[Claim 13]

The method of any one of claims 1 to 12, wherein the pharmaceutically acceptable salt of lenvatinib is lenvatinib mesylate.