(Distribution of somatic mutations in STK11, Catalogue of Somatic Mutations in Cancer, Wellcome Trust Genome Campus, Hinxton, Cambridge).

[0011] Citation or identification of any reference in Section 2 of this application is not to be construed as an admission that the reference is prior art to the present application.

4. SUMMARY

[0012] In one aspect, the present invention refers to the use of a TOR kinase inhibitor in the manufacture of a medicament for treating non-small cell lung carcinoma, in a patient having non-small cell lung carcinoma characterized by a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, relative to wild type, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In another aspect, the present invention refers to an *in vitro* method for predicting the likelihood of a patient having non-small cell lung carcinoma being responsive to TOR kinase inhibitor therapy, comprising screening said patient's carcinoma for the presence of a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, relative to wild type, wherein the presence of LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation predicts an increased likelihood that TOR kinase inhibitor therapy will treat said non-small cell lung carcinoma or cervical cancer, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In yet another aspect, the present invention refers to an *in vitro* method for predicting therapeutic efficacy of treatment of a patient having non-small cell lung carcinoma with a TOR kinase inhibitor, comprising screening said patient's carcinoma or cancer for the presence of a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, relative to wild type, wherein the presence of LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In yet another aspect, the present invention refers to the use of a TOR kinase inhibitor and use of one or more agents that module AMP levels, glucose uptake, metabolism or a stress response in the manufacture of a medicament for treating non- small cell lung carcinoma, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl) -3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically

acceptable salt, stereoisomer, or tautomer thereof. In yet another aspect, the present invention refers to a kit comprising one or more containers filled with a TOR kinase inhibitor or a pharmaceutical composition thereof, reagents for detecting a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, an AMPK gene loss, AMPK protein loss, AMPK gene mutation, or AMPK protein mutation, or both, relative to wild type, in a patient's cancer or in a patient having a tumor syndrome and instructions for detecting LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, AMPK gene loss, AMPK protein loss, AMPK gene mutation, or AMPK protein mutation, or both, in a patient's cancer or in a patient having a tumor syndrome, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. Provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor to a patient having a cancer or a tumor syndrome characterized by a LKB1 gene or protein loss or mutation, relative to that of a control patient or wild type.

[0013] Further provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, comprising screening a patient's cancer for the presence of LKB1 gene or protein loss or mutation relative to that of a control patient or wild type and administering an effective amount of a TOR kinase inhibitor to the patient having a cancer characterized by the LKB1 gene or protein loss or mutation.

[0014] Further provided herein are methods for detecting LKB1 gene or protein loss or mutation in a patient's ("test patient") cancer, for example non-small cell lung carcinoma or cervical cancer, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of LKB1 mRNA expression, the level of LKB1 protein expression, determining the methylation status of the LKB1 gene or otherwise identifying the presence of gene or protein loss or mutation (e.g., by direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss, or immunohistochemistry (IHC), immunofluorescence (IF) or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a LKB1 gene or protein loss or mutation (wild type); wherein a change in LKB1 mRNA expression, LKB1 protein expression, LKB1 mRNA structure, LKB1 gene methylation status and/or LKB1 protein structure in the biological sample

expression, LKB1 protein expression, LKB1 mRNA structure, LKB1 gene methylation status and/or LKB1 protein structure in the biological sample from the test patient, relative to that of the control patient or wild-type, indicates the presence of LKB1 gene or protein loss or mutation in the test patient.

[0019] Further provided herein are methods for predicting the likelihood of a patient having a tumor syndrome, for example Peutz-Jeghers Syndrome, being responsive to TOR kinase inhibitor therapy, comprising screening said patient for the presence of LKB1 gene or protein loss or mutation relative to that of a control patient or wild type, wherein the presence of LKB1 gene or protein loss or mutation predicts an increased likelihood that TOR kinase inhibitor therapy will treat said tumor syndrome.

[0020] Further provided herein are methods for predicting therapeutic efficacy of treatment of a patient having a tumor syndrome, for example Peutz-Jeghers Syndrome, with a TOR kinase inhibitor, comprising screening said patient for the presence of LKB1 gene or protein loss or mutation relative to that of a control patient or wild type, wherein the presence of LKB1 gene or protein loss or mutation in the patient is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor.

[0021] Provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor to a patient having a cancer or a tumor syndrome characterized by AMPK gene or protein loss or mutation, relative to that of a control patient or wild type.

[0022] Provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor to a patient having a cancer or a tumor syndrome characterized by a reduced level of phospho-AMPK (pAMPK) protein and/or AMPK activity relative to that of a control patient or wild type. In one example, the pAMPK is pAMPK T172.

[0023] Further provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, comprising screening a patient's

cancer for the presence of AMPK gene or protein loss or mutation relative to that of a control patient or wild type, and administering an effective amount of a TOR kinase inhibitor to the patient having a cancer characterized by the AMPK gene or protein loss or mutation.

[0024] Further provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, comprising screening a patient's cancer for the presence of a reduced level of pAMPK protein and/or AMPK activity relative to that of a control patient or wild type, and administering an effective amount of a TOR kinase inhibitor to the patient having a cancer characterized by a reduced level of pAMPK protein and/or AMPK activity. In one example, the pAMPK is pAMPK T172.

[0025] Further provided herein are methods for detecting AMPK gene or protein loss or mutation in a patient's ("test patient") cancer, for example non-small cell lung carcinoma or cervical cancer, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of AMPK mRNA expression, the level of AMPK protein expression, determining the methylation status of the AMPK gene, or otherwise identifying the presence of gene or protein loss or mutation (e.g., by direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss, or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a AMPK gene or protein or mutation (wild type); wherein a change in AMPK mRNA expression, AMPK protein expression, AMPK mRNA structure, AMPK gene methylation, and/or AMPK protein structure in the biological sample from the test patient, relative to that of a control patient or wild type, indicates the presence of AMPK gene or protein loss or mutation in the test patient's cancer.

[0026] Further provided herein are methods for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient's ("test patient") cancer, for example non-small cell lung carcinoma or cervical cancer, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of, pAMPK protein expression, the level of AMPK activity, or otherwise measuring the level of pAMPK protein (e.g., immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine the

of a reduced level of pAMPK protein and/or AMPK activity relative to that of a control patient or wild type, wherein the presence a reduced level of pAMPK protein and/or AMPK activity in the patient's cancer is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor.

[0031] Further provided herein are methods for treating or preventing cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor and an effective amount of one or more agents that modulate AMP levels, glucose uptake, metabolism or a stress response to a patient having cancer or a tumor syndrome.

[0032] Further provided herein are pharmaceutical compositions comprising one or more TOR kinase inhibitors and one or more agents that modulate AMP levels, glucose uptake, metabolism or a stress response and a pharmaceutically acceptable carrier, excipient or diluent.

[0033] Further provided herein are kits comprising one or more containers filled with a TOR kinase inhibitor or a pharmaceutical composition thereof, reagents for detecting LKB1 gene or protein loss or mutation, or AMPK gene or protein loss or mutation, or both, in a patient's cancer or in a patient having a tumor syndrome and instructions for detecting LKB1 gene or protein loss or mutation, or AMPK gene or protein loss or mutation, or both, in a patient's cancer or in a patient having a tumor syndrome.

[0034] Further provided herein are kits comprising one or more containers filled with a TOR kinase inhibitor or a pharmaceutical composition thereof, reagents for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient's cancer or in a patient having a tumor syndrome, and instructions for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient's cancer or in a patient having a tumor syndrome.

[0035] In some examples, the TOR kinase inhibitor is a compound as described herein.

[0036] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.