activity on multiple kinases or multiple kinase pathways. Accordingly, there remains a need for new kinase modulators.

[0008] The protein named mTOR (mammalian target of rapamycin), which is also called FRAP, RAFTI or RAPT1), is a 2549-amino acid Ser/Thr protein kinase, that has been shown to be one of the most critical proteins in the mTOR/PI3K/Akt pathway that regulates cell growth and proliferation. Georgakis and Younes *Expert Rev. Anticancer Ther.* 6(1):131-140 (2006). mTOR exists within two complexes, mTORC1 and mTORC2. While mTORC1 is sensitive to rapamycin analogs (such as temsirolimus or everolimus), mTORC2 is largely rapamycin-insensitive. Notably, rapamycin is not a TOR kinase inhibitor. Several mTOR inhibitors have been or are being evaluated in clinical trials for the treatment of cancer. Temsirolimus was approved for use in renal cell carcinoma in 2007 and sirolimus was approved in 1999 for the prophylaxis of renal transplant rejection. Everolimus was approved in 2009 for renal cell carcinoma patients that have progressed on vascular endothelial growth factor receptor inhibitors, in 2010 for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) in patients who require therapy but are not candidates for surgical resection, and in 2011 for progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. There remains a need for additional TOR kinase inhibitors.

[0009] 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.

3. SUMMARY

[0010] In ~~the first~~one aspect, the present invention refers to use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for treating triple negative breast cancer or hormone receptor positive breast cancer in a patient, wherein said medicament is suitable to be administered at about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof. In one example, disclosed herein is ~~the present invention refers to~~ the use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for treating triple negative breast cancer or hormone receptor positive breast cancer in a patient. In another aspect, the present invention refers to use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of a patient, wherein said patient is having triple negative breast cancer or hormone receptor positive breast cancer, wherein said medicament is suitable to be administered at about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

In ~~the second aspect~~another example, ~~the present invention refers to~~disclosed herein is the use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of a patient, wherein said patient is having triple negative breast cancer or hormone receptor positive breast cancer. In another aspect, the present invention refers to an *in vitro* method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having triple negative breast cancer or hormone receptor positive breast cancer, comprising measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient who was administered about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable

salt, stereoisomer or tautomer thereof, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof. In a further aspect, the present invention refers to a method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having triple negative breast cancer or hormone receptor positive breast cancer, comprising irradiating a skin sample of said patient, who was administered about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, with UV light, measuring the amount of phosphorylated DNA-PK S2056 present in the UV light-irradiated skin sample isolated from said patient and comparing said amount of phosphorylated DNA-PK S2056 to that in a UV light-irradiated skin sample from said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof. In one aspect, the present invention refers to a kit comprising 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof and means for monitoring patient response to administration of said 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, wherein said patient has triple negative breast cancer or hormone receptor positive breast cancer, wherein said patient is to be administered about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

In ~~the third aspect~~yet another example, ~~the present invention refers to~~ disclosed herein is an *in vitro* method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having triple negative breast cancer or hormone receptor positive breast cancer, comprising measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient who was administered an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

In the fourth aspect, the present invention refers to a method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having triple negative breast cancer or hormone receptor positive breast cancer, comprising irradiating a skin sample of said patient, who was administered an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, with UV light, measuring the amount of phosphorylated DNA-PK S2056 present in the UV light-irradiated skin sample isolated from said patient and comparing said amount of phosphorylated DNA-PK S2056 to that in a UV light-irradiated skin sample from said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

In the fifth aspect, the present invention refers to a kit comprising 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof and means for monitoring patient response to administration of said 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, wherein said patient has triple negative breast cancer or hormone receptor positive breast cancer.

Disclosed herein are methods for treating or preventing triple negative breast cancer or hormone receptor positive breast cancer, comprising administering an effective amount of a TOR kinase inhibitor to a patient having triple negative breast cancer or hormone receptor positive breast cancer.

[0011] In certain examples, provided herein are methods for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of a patient, comprising

CLAIMS

What is claimed is:

1. Use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for treating triple negative breast cancer or hormone receptor positive breast cancer in a patient, wherein said medicament is suitable to be administered at about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

2. The use of claim 1, wherein the patient has triple negative breast cancer.

3. The use of claim 1, wherein the patient has hormone receptor positive breast cancer.

4. The use of claim 1, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated.

5. The use claim 4, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

6. The use of claim 1, wherein said patient is to be administered a unit dosage form comprising 0.25 mg, 1.0 mg, 5.0 mg, 7.5 mg, or 10 mg of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

7. Use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for improving the Response Evaluation

Criteria in Solid Tumors (RECIST 1.1) of a patient, wherein said patient is having triple negative breast cancer or hormone receptor positive breast cancer, wherein said medicament is suitable to be administered at about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

8. The use of claim 7, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated.

9. The use of claim 8, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

10. An *in vitro* method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having triple negative breast cancer or hormone receptor positive breast cancer, comprising measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient who was administered about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

11. The method of claim 10, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated.

12. The method of claim 11, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

13. A method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having triple negative breast cancer or hormone receptor positive breast cancer, comprising irradiating a skin sample of said patient, who was administered about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, with UV light, measuring the amount of phosphorylated DNA-PK S2056 present in the UV light-irradiated skin sample isolated from said patient and comparing said amount of phosphorylated DNA-PK S2056 to that in a UV light-irradiated skin sample from said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

14. The method of claim 13, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated.

15. The method of claim 14, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

16. A kit comprising 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof and means for monitoring patient response to administration of said 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, wherein said patient has triple negative breast cancer or hormone receptor positive breast cancer, wherein said patient is to be administered about 0.5 mg once per day or about 4 mg, about 8 mg or about 10 mg twice per day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

CLAIMS

What is claimed is:

1. Use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for treating triple negative breast cancer or hormone receptor positive breast cancer in a patient.

2. The use of claim 1, wherein the patient has triple negative breast cancer.

3. The use of claim 1, wherein the patient has hormone receptor positive breast cancer.

4. The use of claim 1, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated.

5. The use claim 4, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

6. The use of claim 1, wherein said patient is to be administered about 0.5 mg/day to about 128 mg/day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

7. The use of claim 6, wherein said patient is to be administered 0.5 mg/day, 1 mg/day, 2 mg/day, 4 mg/day, 8 mg/day, 16 mg/day, 20 mg/day, 30 mg/day, 45 mg/day, 60 mg/day, 90 mg/day, 120 mg/day or 128 mg/day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

8. The use of claim 1, wherein said patient is to be administered a unit dosage form comprising 0.25 mg, 1.0 mg, 5.0 mg, 7.5 mg, or 10 mg of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

9. Use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of a patient, wherein said patient is having triple negative breast cancer or hormone receptor positive breast cancer.

10. The use of claim 9, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated.

11. The use of claim 10, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

12. An *in vitro* method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having triple negative breast cancer or hormone receptor positive breast cancer, comprising measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient who was administered an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

13. The method of claim 12, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated.

14. The method of claim 13, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

15. A method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having triple negative breast cancer or hormone receptor positive breast cancer, comprising irradiating a skin sample of said patient, who was administered an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, with UV light, measuring the amount of phosphorylated DNA-PK S2056 present in the UV light-irradiated skin sample isolated from said patient and comparing said amount of phosphorylated DNA-PK S2056 to that in a UV light-irradiated skin sample from said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

16. The method of claim 15, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated.

17. The method of claim 16, wherein the triple negative breast cancer or hormone receptor positive breast cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

18. A kit comprising 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof and means for monitoring patient response to administration of said 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, wherein said patient has triple negative breast cancer or hormone receptor positive breast cancer.