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 aspect, 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 ~~a TOR kinase inhibitor~~ in the manufacture of a medicament for treating E-twenty six (ETS) overexpressing castration-resistant prostate cancer.

In the second aspect, 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 ~~a TOR kinase inhibitor~~ in the manufacture of a medicament for improving the Prostate-Specific Antigen Working Group 2 (PSAWG2) Criteria for prostate cancer of a patient, wherein said patient is having E-twenty six (ETS) overexpressing castration-resistant prostate cancer.

In the third aspect, ~~the present invention refers to an *in vitro* method for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample isolated of a patient having E-twenty six (ETS) overexpressing castration-resistant prostate cancer, wherein said patient was administered an effective amount of a TOR kinase inhibitor, wherein the method comprises comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample isolated of a patient obtained prior to~~

~~and after administration of said TOR kinase inhibitor, wherein less phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said TOR kinase inhibitor relative to the~~

~~amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.~~

~~In the fourth aspect, the present invention refers to an *in vitro* method for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having E-twenty six (ETS) overexpressing castration-resistant prostate cancer, wherein said patient was administered an effective amount of a TOR kinase inhibitor, wherein the method comprises comparing the amount of phosphorylated DNA-PK in a biological sample isolated of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated DNA-PK in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated DNA-PK in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.~~

~~In the fifth 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 E-twenty six (ETS) overexpressing castration-resistant prostate 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~~a TOR kinase inhibitor~~, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of a 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~~TOR kinase inhibitor~~.

In the fourth~~sixth~~ aspect, the present invention refers to an *in vitro* method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having E-twenty six (ETS) overexpressing castration-resistant prostate cancer, comprising measuring the amount of phosphorylated DNA-PK S2056 present in the 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~~a TOR kinase inhibitor~~, and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to administration of an effective amount of a 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~~TOR kinase inhibitor~~.

In the fifthseventh 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 a TOR kinase inhibitor 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 thereofTOR kinase inhibitor, wherein said patient has E-twenty six (ETS) overexpressing castration-resistant prostate cancer.

Further described herein are methods for treating or preventing E-twenty six (ETS) overexpressing castration-resistant prostate cancer comprising administering an effective amount of a TOR kinase inhibitor to a patient having ETS overexpressing castration-resistant prostate cancer.

[0011] In certain examples, provided herein are methods for improving the Prostate-Specific Antigen Working Group 2 (PSAWG2) Criteria for prostate cancer of a patient, comprising administering an effective amount of a TOR kinase inhibitor to a patient having ETS overexpressing castration-resistant prostate cancer.

[0012] In some examples, the TOR kinase inhibitor is a compound as described herein.

[0013] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

4. DETAILED DESCRIPTION

DEFINITIONS

[0014] An "alkyl" group is a saturated, partially saturated, or unsaturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms, typically from 1 to 8 carbons or, in some embodiments, from 1 to 6, 1 to 4, or 2 to 6 or carbon atoms. Representative alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl and the like. Examples of unsaturared alkyl groups include, but are not limited to, vinyl, allyl, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, $-C\equiv CH$, $-C\equiv C(CH_3)$, $-C\equiv C(CH_2CH_3)$, $-CH_2C\equiv CH$, $-CH_2C\equiv C(CH_3)$ and $-CH_2C\equiv C(CH_7CH_3)$, among others. An alkyl group can be substituted or unsubstituted. In certain embodiments, when the alkyl groups described herein are said to be "substituted," they may be substituted with any substituent or substituents as those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano;

thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; sulfonyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aralkoxyamine; N-oxide;

CLAIMS

What is claimed is:

1. Use of ~~a TOR kinase inhibitor~~ 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 E-twenty six (ETS) overexpressing castration-resistant prostate cancer.

2. The use of claim 1, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate cancer is that in which the PI3K/mTOR pathway is activated.

3. The use of claim 2, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate 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.

4. The use of claim 1, wherein said medicament is to be administered in an amount of 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 ~~a TOR kinase inhibitor~~.

5. The use of claim 4, wherein said medicament is to be administered in an amount of 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 ~~a TOR kinase inhibitor~~.

6. The use of claim 1, wherein said medicament is to be administered in 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 ~~a TOR kinase inhibitor~~.

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 ~~a TOR kinase inhibitor~~ in the manufacture of a medicament for improving the Prostate-Specific Antigen Working Group 2 (PSAWG2) Criteria for prostate

cancer of a patient, wherein said patient is having E-twenty six (ETS) overexpressing castration-resistant prostate cancer.

8. The use of claim 7, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate cancer is that in which the PI3K/mTOR pathway is activated.

9. The use of claim 8, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate 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 inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample isolated of a patient having E-twenty six (ETS) overexpressing castration-resistant prostate cancer, wherein said patient was administered an effective amount of a TOR kinase inhibitor, wherein the method comprises comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample isolated of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.~~

~~11. The method of claim 10, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate cancer is that in which the PI3K/mTOR pathway is activated.~~

~~12. The method of claim 11, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate 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. An *in vitro* method for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having E-twenty six (ETS) overexpressing castration-resistant prostate cancer, wherein said patient was administered an effective amount of a TOR kinase inhibitor, wherein the method comprises comparing the amount of phosphorylated DNA-PK in a biological sample isolated of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein~~

~~less phosphorylated DNA-PK in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated DNA-PK in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.~~

~~14. The method of claim 13, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate cancer is that in which the PI3K/mTOR pathway is activated.~~

~~15. The method of claim 14, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate 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.~~10. An *in vitro* method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having E-twenty six (ETS) overexpressing castration-resistant prostate 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 ~~a TOR kinase inhibitor~~, 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 ~~a TOR kinase inhibitor~~.

~~17.~~11. The method of claim 10~~16~~, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate cancer is that in which the PI3K/mTOR pathway is activated.

~~18.~~12. The method of claim 11~~17~~, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate 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.

~~19.~~13. An *in vitro* method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having E-twenty six (ETS) overexpressing castration-resistant prostate cancer, comprising measuring the amount of phosphorylated DNA-PK S2056 present in the 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

~~a TOR kinase inhibitor~~, and comparing said amount of phosphorylated DNA-PK S2056 to that in a 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 ~~a TOR kinase inhibitor~~.

~~20.~~14. The method of claim 13~~19~~, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate cancer is that in which the PI3K/mTOR pathway is activated.

~~21.~~15. The method of claim 14~~20~~, wherein the E-twenty six (ETS) overexpressing castration-resistant prostate 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.

~~22.~~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 ~~a TOR kinase inhibitor~~ 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 ~~TOR kinase inhibitor~~, wherein said patient has E-twenty six (ETS) overexpressing castration-resistant prostate cancer.