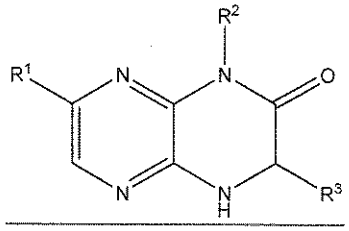
[0008] The protein named mTOR (mammalian target of rapamycin), which is also called FRAP, RAFTI or RAPT1), is a 2549-amino acid Ser/Thr protein kinase, that has been shown to be one of the most critical proteins in the mTOR/PI3K/Akt pathway that regulates cell growth and proliferation. Georgakis and 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 TOR kinase inhibitors that inhibit both mTORC1 and mTORC2 complexes.

[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 one aspect, there is provided a use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog in the manufacture of a medicament for treating advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof, wherein:

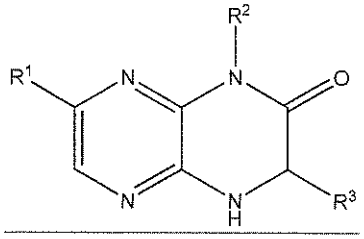
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl.

Provided herein are methods for treating or preventing advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor and an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer.

[0011] In another aspect, there is provided a use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog in the manufacture of a medicament for achieving a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of complete response, partial response or stable disease in a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof, wherein:

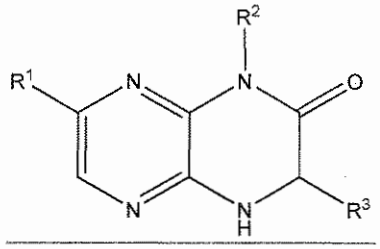
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl.

In certain ~~embodiments~~examples, provided herein are methods for achieving a Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1) of complete response, partial response or stable disease in a patient having advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to said patient.

[0012] In one aspect, there is provided Use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog in the manufacture of a medicament for increasing survival without tumor progression of a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl.

In certain ~~embodiments~~examples, provided herein are methods for increasing survival without tumor progression of a patient having advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to said patient.

[0013] In certain ~~embodiments~~examples, the TOR kinase inhibitor is a compound as described herein.

[0014] The present ~~embodiments~~disclosure can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 depicts the viability dose-response curves and isobolograms for Compound 1 and 5-azacitidine for H1755 cells, and the synergy seen for the combination treatment, for 2 combination ratios.

[0016] Figure 2 depicts the viability dose-response curves and isobolograms for Compound 1 and erlotinib for H1755 cells, and the synergy seen for the combination treatment, for 2 combination ratios.

[0017] Figure 3 depicts: A. Impact of sequence of addition and ratio on CI values. CI values of all combinations from each of the three sequences of addition were compared by t-test. Sim: Simultaneously addition of both compounds; SeqM1: Compound 1 first followed by addition of azacitidine; SeqM2: azacitidine first followed by addition of Compound 1. B. Different ratios of azacitidine and Compound 1 do not significantly impact CI values in SeqM2 addition.

[0018] Figure 4 depicts: A. Sequence of addition has no impact on CI values for Compound 1 and erlotinib combination. CI values of all combinations from each of the three sequences of addition were compared by t-test. Sim: Simultaneously addition of both compounds; SeqM1: Compound 1 first followed by addition of azacitidine; SeqM2: azacitidine first followed by addition of Compound 1. B. Different ratios of azacitidine and Compound 1 significantly impact CI values.

CLAIMS

What is claimed is:

1. A method for treating advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer.

2. The method of claim 1, comprising administration of a TOR kinase inhibitor in combination with an effective amount of erlotinib to a patient having advanced non-small cell lung cancer.

3. The method of claim 1, comprising administration of a TOR kinase inhibitor in combination with an effective amount of a cytidine analog to a patient having advanced non-small cell lung cancer.

4. The method of claim 3, wherein the cytidine analog is azacitidine

5. The method of claim 4, wherein the azacitidine is oral azacitidine.

6. A method for achieving a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of complete response, partial response or stable disease in a patient having advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to said patient.

7. The method of claim 6, comprising administration of a TOR kinase inhibitor in combination with an effective amount of erlotinib to a patient having advanced non-small cell lung cancer.

8. The method of claim 6, comprising administration of a TOR kinase inhibitor in combination with an effective amount of a cytidine analog to a patient having advanced non-small cell lung cancer.

9. The method of claim 8, wherein the cytidine analog is azacitidine.

10. The method of claim 9, wherein the azacitidine is oral azacitidine.

11. A method for increasing survival without tumor progression of a patient having advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to said patient.

12. The method of claim 11, comprising administration of a TOR kinase inhibitor in combination with an effective amount of erlotinib to a patient having advanced non-small cell lung cancer.

13. The method of claim 11, comprising administration of a TOR kinase inhibitor in combination with an effective amount of a cytidine analog to a patient having advanced non-small cell lung cancer.

14. The method of claim 13, wherein the cytidine analog is azacitidine.

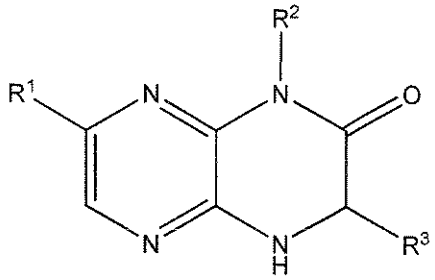
15. The method of claim 14, wherein the azacitidine is oral azacitidine.

16. The method of any one of claims 1 – 15, wherein the TOR kinase inhibitor is a compound of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (II), (IIa), (IIb), (IIc), (IId), (III), or (IV).

17. The method of any one of claims 1 – 15, wherein the TOR kinase inhibitor is a compound from Table A, B, C or D.

What is claimed is:

1. Use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog in the manufacture of a medicament for treating advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl.

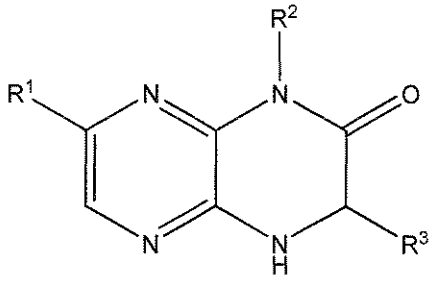
2. The use of claim 1, wherein a TOR kinase inhibitor is administered in combination with an effective amount of erlotinib to a patient having advanced non-small cell lung cancer.

3. The use of claim 1, wherein a TOR kinase inhibitor is administered in combination with an effective amount of a cytidine analog to a patient having advanced non-small cell lung cancer.

4. The use of claim 3, wherein the cytidine analog is azacitidine

5. The use of claim 4, wherein the azacitidine is oral azacitidine.

6. Use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog in the manufacture of a medicament for achieving a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of complete response, partial response or stable disease in a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl.

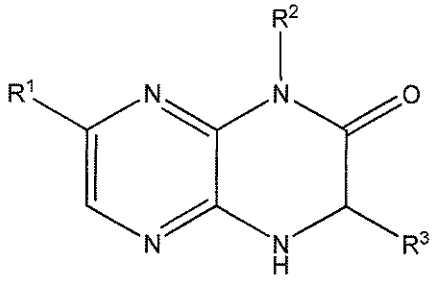
7. The use of claim 6, wherein a TOR kinase inhibitor is administered in combination with an effective amount of erlotinib to a patient having advanced non-small cell lung cancer.

8. The use of claim 6, wherein a TOR kinase inhibitor is administered in combination with an effective amount of a cytidine analog to a patient having advanced non-small cell lung cancer.

9. The use of claim 8, wherein the cytidine analog is azacitidine.

10. The use of claim 9, wherein the azacitidine is oral azacitidine.

11. Use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog in the manufacture of a medicament for increasing survival without tumor progression of a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl.

12. The use of claim 11, wherein a TOR kinase inhibitor is administered in combination with an effective amount of erlotinib to a patient having advanced non-small cell lung cancer.

13. The use of claim 11, wherein a TOR kinase inhibitor is administered in combination with an effective amount of a cytidine analog to a patient having advanced non-small cell lung cancer.

14. The use of claim 13, wherein the cytidine analog is azacitidine.

15. The use of claim 14, wherein the azacitidine is oral azacitidine.

16. The use of any one of claims 1 – 15, wherein the TOR kinase inhibitor is a compound from Table D.