Claims

1. Use of a bi-steric inhibitor of mTOR in the manufacture of a medicament for delaying or preventing acquired resistance to a RAS inhibitor in a subject in need thereof, wherein an effective amount of the bi-steric inhibitor of mTOR is to be administered to the subject, wherein the subject has already received or will receive administration of the RAS inhibitor, wherein the effective amount is an amount effective to delay or prevent acquired resistance to the RAS inhibitor in the subject.

2. Use of a bi-steric inhibitor of mTOR in the manufacture of a medicament for treating acquired resistance to a RAS inhibitor in a subject, wherein an effective amount of the bi-steric inhibitor of mTOR is to be administered to the subject, wherein the effective amount is an amount effective to treat acquired resistance to the RAS inhibitor in the subject.

3. The use claim 1 or claim 2, wherein the medicament is to be administered with an effective amount of the RAS inhibitor.

4. The use of any one of claims 1-3, wherein the RAS inhibitor targets a specific RAS mutation.

5. The use of any one of claims 1-4, wherein the RAS inhibitor targets a KRAS mutation.

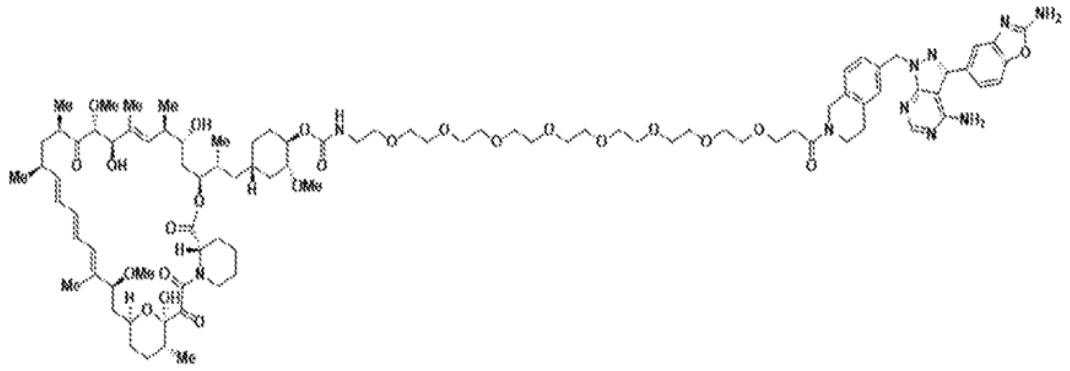
6. The use of any one of claims 1-5, wherein the RAS inhibitor targets the KRASG12C mutation.

7. The use of any one of claims 1-6, wherein the RAS inhibitor is a KRAS(OFF) inhibitor.

8. The use of claim 7, wherein the KRAS(OFF) inhibitor is selected from AMG 510, MRTX849, JDQ443 and MRTX1133, or a pharmaceutically acceptable salt thereof.

9. The use of any one of claims 1-8, wherein the bi-steric inhibitor of mTOR is RM- 006, also known as RMC-6272, or RMC-5552, or a pharmaceutically acceptable salt thereof.

10. The use of any one of claims 1-9, wherein the bi-steric inhibitor of mTOR is a compound having the formula



or a stereoisomer or tautomer thereof.

11. The use of any one of claims 1-6 or 9-10, wherein the RAS inhibitor is a KRAS(ON) inhibitor.

12. The use of claim 11, wherein the KRAS(ON) inhibitor is a $KRAS^{G12C}$ (ON) inhibitor.

13. The use of any one of claims 1-12, wherein the medicament is for treating or preventing a cancer.

14. The use of 13, wherein the cancer comprises a $KRAS^{G12C}$ mutation.

15. The use of claim 13 or 14, wherein the cancer comprises co-occurring $KRAS^{G12C}$ and STK11 mutations.

16. The use of any one of claims 13-15, wherein the cancer is a Non-Small Cell Lung Cancer (NSCLC) or a colorectal cancer.

17. The use of any one of claims 13-16, wherein the cancer comprises co-occurring $KRAS^{G12C}$ and $PIK3CA^{E545K}$ mutations.

18. The use of any one of claims 13-17, wherein the cancer is a colorectal cancer.

19. The use of any one of claims 1-18, wherein the medicament results in tumor regression.

20. The use of any one of claims 1-18, wherein the medicament results in tumor apoptosis.

21. Use of a bi-steric inhibitor of mTOR in combination with a RAS inhibitor in the manufacture of a medicament for treating a subject having a cancer, wherein an effective amount of the bi-steric inhibitor of mTOR in combination with a RAS inhibitor is to be administered to the subject.

22. The use of claim 21, wherein the RAS inhibitor targets a specific RAS mutation.

23. The use of claim 21 or 22, wherein the RAS inhibitor targets a KRAS mutation.

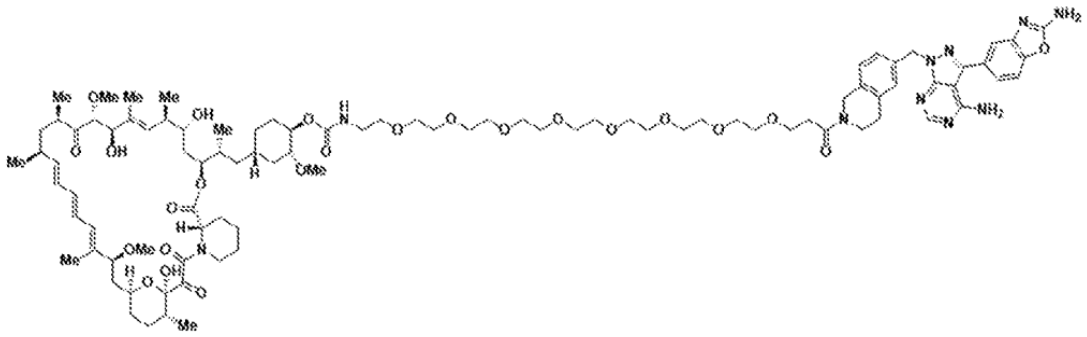
24. The use of any one of claims 21-23, wherein the RAS inhibitor targets the $KRAS^{G12C}$ mutation.

25. The use of any one of claims 21-24, wherein the RAS inhibitor is a KRAS(OFF) inhibitor.

26. The use of claim 25, wherein the KRAS(OFF) inhibitor is selected from AMG 510, MRTX849, JDQ443 and MRTX1133, or a pharmaceutically acceptable salt thereof.

27. The use of any one of claims 21-26, wherein the bi-steric inhibitor of mTOR is RM- 006, also known as RMC-6272, or RMC-5552, or a pharmaceutically acceptable salt thereof.

28. The use of any one of claims 21-26, wherein the bi-steric inhibitor of mTOR is a compound having the formula



or a stereoisomer or tautomer thereof.

29. The use of any one of claims 21-24, 27 or 28, wherein the RAS inhibitor is a KRAS(ON) inhibitor.

30. The use of claim 29, wherein the KRAS(ON) inhibitor is a $KRAS^{G12C}$ (ON) inhibitor.

31. The use of any one of claims 21-30, wherein the cancer comprises a $KRAS^{G12C}$ mutation.

32. The use of any one of claims 21-31, wherein the cancer comprises co-occurring $KRAS^{G12C}$ and STK11 mutations.

33. The use of any one of claims 21-32, wherein the cancer is a Non-Small Cell Lung Cancer (NSCLC).

34. The use of any one of claims 21-33, wherein the cancer comprises co-occurring $KRAS^{G12C}$ and $PIK3CA^{E545K}$ mutations.

35. The use of any one of claims 21-32 or 34, wherein the cancer is a colorectal cancer.

36. The use of any one of claims 21-35, wherein the method results in tumor regression.

37. The use of any one of claims 21-36, wherein the method results in tumor apoptosis.

38. A method of inducing apoptosis of a tumor cell comprising contacting the tumor cell with an effective amount of a bi-steric inhibitor of mTOR in combination with a RAS inhibitor, wherein the effective amount is an amount effective to induce apoptosis of the tumor cell.

39. The use of any one of claims 1-37 or the method of claim 38, wherein the method results in an improved lifespan for the subject as compared to the lifespan of a similar subject that has not received a treatment with the RAS inhibitor and the bi-steric mTOR inhibitor.