SUMMARY

The disclosure is based on the observation that the combination of eribulin mesylate and an mTOR inhibitor, everolimus, shows improved (e.g., synergistic) antitumor effects. Therefore, the present invention features methods of preventing and treating cancer by use of the combination of eribulin (e.g., eribulin mesylate) and one or more mTOR inhibitors (e.g., everolimus).

When the term "eribulin" is used herein, it should be considered as indicating eribulin or a pharmaceutically acceptable salt thereof (such as eribulin mesylate), unless the context indicates otherwise. Similarly, when the term "mTOR inhibitor" (or the name of a specific mTOR inhibitor, such as everolimus) is used herein, it should be considered as indicating the mTOR inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, as applicable, unless the context indicates otherwise.

The disclosure provides methods for treating a subject (e.g., a human patient) having or at risk of developing cancer. These methods include administering to the subject (i) eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate), and (ii) an inhibitor of mammalian target of rapamycin (mTOR) (e.g., everolimus, ridaforolimus, or temsirolimus) or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof. The subject can be diagnosed with a cancer, in treatment for cancer, or in post-therapy recovery from cancer. In various embodiments, the cancer can be a primary tumor or a metastasis, and can optionally be a solid tumor. In further embodiments, the cancer is selected from the group consisting of breast cancer, lung cancer, pancreatic cancer, primitive neuroectodermal tumors, lung cancer, ovarian cancer, endometrial cancer, pharyngeal cancer, esophageal cancer, and sarcoma.

In an aspect, there is provided the use of (i) eribulin or a pharmaceutically acceptable salt thereof, and (ii) an inhibitor of mammalian target of rapamycin (mTOR) or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, in the manufacture of a medicament for treating cancer in a subject.

Eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) can be administered by intravenous infusion for, e.g., 1 to about 20 minutes, e.g., for about 2 to about 5 minutes. The amount of eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) can be in the range of about 0.1 mg/m^2 to about 20 mg/m^2 (e.g., 1.4 mg/m^2 or 1.1 mg/m^2), optionally administered once daily on each of days 1 and 8 of a 21-day cycle, or once daily on each of days 1 and 15 of a 28-day cycle.

The mTOR inhibitor (e.g., everolimus, ridaforolimus, or temsirolimus) can be administered orally in, e.g., an amount in the range of about 0.1 mg to about 30 mg (e.g., 10 mg), and can optionally be administered once daily during a 21-day cycle or a 28-day cycle.

Eribulin or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor (e.g., everolimus, ridaforolimus, or temsirolimus), or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, can be administered substantially simultaneously or sequentially. For example, eribulin or a pharmaceutically acceptable salt thereof can be administered prior to an mTOR inhibitor (e.g., everolimus, ridaforolimus, or temsirolimus), or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof.

CLAIMS

1. Use of (i) eribulin or a pharmaceutically acceptable salt thereof, and (ii) an inhibitor of mammalian target of rapamycin (mTOR) or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, in the manufacture of a medicament for treating cancer in a subject.

2. The use of claim 1, wherein said subject is a human patient.

3. The use of claim 1, wherein said subject is diagnosed with a cancer, or in treatment for cancer.

4. The use of claim 1, wherein said cancer is a primary tumor.

5. The use of claim 1, wherein said cancer is a metastasis.

6. The use of claim 1, wherein said cancer is a solid tumor.

7. The use of claim 1, wherein said cancer is selected from the group consisting of breast cancer, lung cancer, pancreatic cancer, primitive neuroectodermal tumors, ovarian cancer, endometrial cancer, pharyngeal cancer, esophageal cancer, and sarcoma.

8. The use of claim 7, wherein said cancer is selected from breast cancer and lung cancer.

9. The use of claim 1, wherein said pharmaceutically acceptable salt of eribulin is eribulin mesylate.

10. The use of claim 1, wherein said eribulin or said pharmaceutically acceptable salt thereof is to be administered by intravenous infusion.

11. The use of claim 10, wherein said intravenous infusion is for 1 to 20 minutes.

12. The use of claim 11, wherein said intravenous infusion is for 2 to 5 minutes.

13. The use of claim 1, wherein said eribulin or said pharmaceutically acceptable salt thereof is to be administered in an amount in the range of 0.1 mg/m^2 to 20 mg/m^2.

14. The use of claim 13, wherein said eribulin or said pharmaceutically acceptable salt thereof is to be administered in an amount of 1.1 mg/m^2 or 1.4 mg/m^2.

15. The use of claim 1, wherein said eribulin or said pharmaceutically acceptable salt thereof is to be administered once on each of days 1 and 8 of a 21-day cycle, or each of days 1 and 15 of a 28-day cycle.

16. The use of claim 1, wherein said mTOR inhibitor is selected from the group consisting of everolimus, ridaforolimus, and temsirolimus, and pharmaceutically acceptable salts, hydrates, solvates, or amorphous solid thereof.

17. The use of claim 1, wherein said mTOR inhibitor is everolimus or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof.

18. The use of claim 17, wherein said everolimus or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof is to be administered orally.

19. The use of claim 18, wherein said everolimus or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof is to be administered in an amount in the range of 0.1 mg to 30 mg.

20. The use of claim 19, wherein said everolimus or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof is to be administered in an amount of 10 mg.

21. The use of claim 1, wherein said mTOR inhibitor, or said pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, is to be administered once daily during a 21-day cycle or a 28-day cycle.

22. The use of claim 1, wherein said eribulin or said pharmaceutically acceptable salt thereof, and said mTOR inhibitor, or said pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, are to be administered substantially simultaneously or sequentially.

23. The use of claim 22, wherein said eribulin or said pharmaceutically acceptable salt thereof is to be administered prior to said mTOR inhibitor, or said pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof.

24. The use of claim 1, wherein said eribulin or said pharmaceutically acceptable salt thereof, and said mTOR inhibitor, or said pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, are to be administered as sole anti-cancer agents.