SUMMARY ~~OF THE INVENTION~~

The ~~invention~~ 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 ~~invention~~ 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 a subject having or at risk of developing of cancer.

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.

Furthermore, eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate), and an mTOR inhibitor (e.g., everolimus, ridaforolimus, or temsirolimus), or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, can optionally be administered as sole anti-cancer agents.

Treatment according to the methods of the ~~invention~~disclosure: (i) reduces the number of cancer cells; (ii) reduces tumor volume; (iii) increases tumor regression rate; (iv) reduces or slows cancer cell infiltration into peripheral organs; (v) reduces or slows tumor metastasis; (vi) reduces or inhibits tumor growth; (vii) prevents or delays occurrence and/or recurrence of the cancer and/or extends disease- or tumor-free survival time;

(viii) increases overall survival time; (ix) reduces the frequency of treatment; and/or (x) relieves one or more of symptoms associated with the cancer.

The ~~invention~~ disclosure also provides methods for decreasing the size of a tumor in a subject (e.g., a human patient). These methods include administering to the subject (i) eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate), and (ii) an mTOR inhibitor (e.g., everolimus, ridaforolimus, or temsirolimus) or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof. These methods can involve the administration regimens and cancers described above and elsewhere herein.

In another aspect ,there is provided the use of (i) eribulin or a pharmaceutically acceptable salt thereof, and (ii) an mTOR inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, in the manufacture of a medicament for decreasing the size of a tumor.

Also included in the ~~invention~~disclosure are kits for use in preventing or treating cancer or decreasing tumor size (also see, e.g., the effects listed above). The kits can include (i) eribulin or a pharmaceutically acceptable salt thereof, and (ii) an mTOR inhibitor (e.g., everolimus, ridaforolimus, or temsirolimus) or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, optionally in dosage form.

In another aspect, there is provided a kit for use in treating cancer or decreasing tumor size, the kit comprising (i) eribulin or a pharmaceutically acceptable salt thereof, and (ii) an mTOR inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof.

The ~~invention~~ disclosure further includes pharmaceutical compositions including the agents noted herein for use in preventing and treating the diseases and conditions noted herein. Furthermore, the invention includes use of the agents noted herein for preparing medicaments and/or for preventing or treating these diseases and conditions.

The methods of the ~~invention~~ disclosure provide improved efficacy against cancer. For example, the combination treatment methods described herein can be used to obtain synergistic effects in which, for example, the effects are greater than the sum of the effects of the drugs administered individually, as can be determined by those of skill in the art. Additive effects are also beneficial.

Other features and advantages of the ~~invention~~ disclosure will be apparent from the following detailed description, drawings, and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the effect of treatment with E7389 on mean body weight of female athymic nude mice implanted SC with MX-1 mammary tumor xenografts.

Figure 2 is a graph showing the response of SC implanted MX-1 mammary tumor xenografts to treatment with E7389.

Figure 3 is a graph showing the effect of treatment with everolimus on mean body weight of female athymic nude mice implanted SC with MX-1 mammary tumor xenografts.

Figure 4 is a graph showing the response of SC implanted MX-1 mammary tumor xenografts to treatment with everolimus.

Figure 5 is a graph showing the effect of treatment with E7389 in combination with everolimus (40 mg/kg/dose) on mean body weight of female athymic nude mice implanted SC with MX-1 mammary tumor xenografts.

Figure 6 is a graph showing the effect of treatment with E7389 in combination with everolimus (20 mg/kg/dose) on mean body weight of female athymic nude mice implanted SC with MX-1 mammary tumor xenografts.

Figure 7 is a graph showing the response of SC implanted MX-1 mammary tumor xenografts to treatment with E7389 (0.6 mg/kg/inj) in combination with everolimus.

Figure 8 is a graph showing the response of SC implanted MX-1 mammary tumor xenografts to treatment with E7389 (0.4 mg/kg/inj) in combination with everolimus.

CLAIMS

1. ~~A method for treating a subject having or at risk of developing cancer, the method comprising administering to the subject~~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 a subject having or at risk of developing cancer.

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

3. The ~~method~~ use of claim 1, wherein said subject is diagnosed with a cancer, in treatment for cancer, or in post-therapy recovery from cancer.

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

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

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

7. The ~~method~~ use of claim 1, wherein said 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.

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

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

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

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

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

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

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

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

18. The ~~method~~ 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 ~~method~~ 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 about 0.1 mg to about 30 mg.

20. The ~~method~~ 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 about 10 mg.

21. The ~~method~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ 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.

25. The ~~method~~ use of claim 24, wherein said pharmaceutically acceptable salt of eribulin is eribulin mesylate and/or said mTOR inhibitor is everolimus.

26. The ~~method~~ use of claim 1, wherein said treating: (i) reduces the number of cancer cells; (ii) reduces tumor volume; (iii) increases tumor regression rate; (iv) reduces or slows cancer cell infiltration into peripheral organs; (v) reduces or slows tumor metastasis; (vi) reduces or inhibits tumor growth; (vii) prevents or delays occurrence and/or recurrence of the cancer and/or extends disease- or tumor-free survival time; (viii) increases overall survival time; (ix) reduces the frequency of treatment; and/or (x) relieves one or more of symptoms associated with the cancer.

27. ~~A method for decreasing the size of a tumor in a subject, the method comprising administering to the subject~~ Use of (i) eribulin or a pharmaceutically acceptable salt thereof, and (ii) an mTOR inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, in the manufacture of a medicament for decreasing the size of a tumor.

28. The ~~method~~ use of claim 27, wherein said mTOR inhibitor is everolimus or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof.

29. A kit for use in treating cancer or decreasing tumor size, the kit comprising (i) eribulin or a pharmaceutically acceptable salt thereof, and (ii) an mTOR inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof.

30. The kit of claim 29, wherein said mTOR inhibitor is everolimus or a pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof.

31. The kit of claim 29, wherein said (i) eribulin or said pharmaceutically acceptable salt thereof, and said (ii) mTOR inhibitor or said pharmaceutically acceptable salt, hydrate, solvate, or amorphous solid thereof, are in dosage form.