The methods as defined above provide improved efficacy against cancer. Combination methods in some instances can, for example, be used to obtain synergistic effects in which, for example, the effects are greater than the sum of the effects of drugs administered individually. Combination methods that result in additive effects are also beneficial.

In an aspect, there is provided the use of eribulin or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a subject having breast cancer, the use further comprising (i) a second agent to be subsequently administered to the subject, wherein the second agent is selected from the group consisting of capecitabine, paclitaxel and carboplatin, (ii) the eribulin or pharmaceutically acceptable salt thereof is to be administered as a pre-treatment to the second agent, and (iii) the eribulin or pharmaceutically acceptable salt thereof is to be administered 1, 2, 3, 4, 5 or 6 days or 1-12 weeks before the second agent.

In another aspect, there is provided the use of eribulin or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for decreasing the size of a tumor in a subject having breast cancer, the use further comprising a second agent to be subsequently administered to the subject, wherein (i) the second agent is selected from the group consisting of capecitabine, paclitaxel and carboplatin, (ii) the eribulin or pharmaceutically acceptable salt thereof is to be administered as a pre-treatment to the second agent, and (iii) the eribulin or pharmaceutically acceptable salt thereof is to be administered 1, 2, 3, 4, 5 or 6 days or 1-12 weeks before the second agent.

In another aspect, there is provided the use of eribulin or a pharmaceutically acceptable salt thereof the manufacture of a medicament for increasing the efficacy of an agent, wherein (i) the agent is selected from the group consisting of capecitabine, paclitaxel and carboplatin, (ii) the eribulin or pharmaceutically acceptable salt thereof is to be administered as a pre-treatment to the agent, and (iii) the eribulin or pharmaceutically acceptable salt thereof is to be administered 1, 2, 3, 4, 5 or 6 days or 1-12 weeks before the agent.

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

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the antitumor effect of capecitabine after eribulin treatment in a human breast cancer cell line MDA-MB-231 s.c. xenograft model.

Fig. 2 is a graph showing the antitumor effect of sequential treatment of eribulin and paclitaxel (PTX) in a human breast cancer cell line MDA-MB-231 s.c. xenograft model.

Figs. 3A and 3B are graphs showing the antitumor effect of sequential treatment of eribulin plus carboplatin (CBDCA) and paclitaxel plus carboplatin in a human breast cancer cell line MDA-MB-231 s.c. xenograft model. Fig. 3A shows anti-tumor effect and Fig. 3B shows body weight of sequential treatment.

Fig. 4 is a graph showing the concentration of carboplatin in MDA-MB-231 tumors after treatment with eribulin.

DETAILED DESCRIPTION

The invention provides methods for the prevention and treatment of cancer involving administration of eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) prior to a second (or further) anticancer agent such as, for example, capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based antineoplastic agent (e.g., carboplatin, cisplatin, or oxaliplatin), doxorubicin, or ixabepilone. According to the methods of the invention, eribulin may be administered prior to a second anticancer agent used in the first, second, or third line in the treatment of breast cancer, in the neoadjuvant setting, to enhance the efficacy of the second anticancer agent.

Treatment of cancer according to the methods of the invention, can (i) reduce the number of cancer cells; (ii) reduce tumor volume; (iii) increase tumor regression rate; (iv) reduce or slow cancer cell infiltration into peripheral organs; (v) reduce or slow tumor metastasis; (vi) reduce or inhibit tumor growth; (vii) prevent or delay occurrence and/or recurrence of the cancer and/or extend disease- or tumor-free survival time; (viii) increase overall survival time; (ix) reduce the frequency of treatment; and/or (x) relieve one or more of symptoms associated with the cancer.

Pharmaceutical Compositions, Dosage, and Methods

Pharmaceutical compositions including eribulin and/or the other agents described herein can be prepared using standard methods known in the art, or can be obtained from commercial sources. Typically, eribulin and the other agents used in the invention are included within separate pharmaceutical

CLAIMS

1. Use of eribulin or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a subject having breast cancer, the use further comprising a second agent to be subsequently administered to the subject, wherein (i) the second agent is selected from the group consisting of capecitabine, paclitaxel and carboplatin, (ii) the eribulin or pharmaceutically acceptable salt thereof is to be administered as a pre-treatment to the second agent, and (iii) the eribulin or pharmaceutically acceptable salt thereof is to be administered 1, 2, 3, 4, 5 or 6 days or 1-12 weeks before the second agent.

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 breast cancer, in treatment for breast cancer, or in post-therapy recovery from breast cancer.

4. The use of claim 1, wherein said treatment is to be carried out as neoadjuvant treatment prior to surgery.

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

6. The use of claim 1, wherein said breast cancer is locally advanced.

7. The use of claim 1, wherein said breast cancer is metastatic.

8. The use of claim 1, wherein said breast cancer is estrogen receptor positive or negative, progesterone receptor positive or negative, HER-2 positive or negative, or triple-negative breast 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.

16. The use of claim 1, wherein administration of eribulin or said pharmaceutically acceptable salt thereof is to be completed prior to administration of said second agent.

17. The use of claim 1, wherein administration of eribulin or said pharmaceutically acceptable salt thereof is to be continued after administration of said second agent begins.

18. The use of claim 1, wherein said second agent to be administered is capecitabine.

19. The use of claim 18, wherein said capecitabine is to be administered daily for two weeks, followed by a one-week rest.

20. The use of claim 1, wherein said second agent to be administered is paclitaxel.

21. The use of claim 1, wherein said second agent to be administered is carboplatin.

22. The use of claim 1, wherein 1-8, 2-7, 3-6, or 4-5 doses or complete cycles of eribulin are to be administered prior to 1-8, 2-7, 3-6, or 4-5 doses or complete cycles of said second agent.

23. The 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.

24. Use of eribulin or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for decreasing the size of a tumor in a subject having breast cancer, the use further comprising a second agent to be subsequently administered to the subject, wherein (i) the second agent is selected from the group consisting of capecitabine, paclitaxel and carboplatin, (ii) the eribulin or pharmaceutically acceptable salt thereof is to be administered as a pre-treatment to the second agent, and (iii) the eribulin or pharmaceutically acceptable salt thereof is to be administered 1, 2, 3, 4, 5 or 6 days or 1-12 weeks before the second agent.

25. Use of eribulin or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for increasing the efficacy of an agent, wherein (i) the agent is selected from the group consisting of capecitabine, paclitaxel and carboplatin, (ii) the eribulin or pharmaceutically acceptable salt thereof is to be administered as a pre-treatment to the agent, and (iii) the eribulin or pharmaceutically acceptable salt thereof is to be administered 1, 2, 3, 4, 5 or 6 days or 1-12 weeks before the agent.

26. The use of claim 1, wherein one or more complete cycles of eribulin are to be administered prior to one or more doses or complete cycles of the second agent.