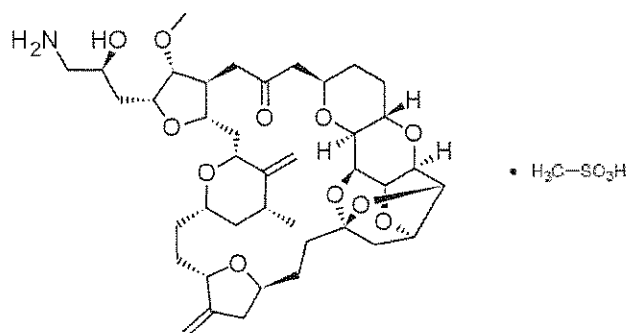




SUMMARY

The disclosure is based in part on observations that administration of eribulin mesylate prior to certain other agents (such as capecitabine, paclitaxel, and carboplatin), shows improved (e.g., synergistic) antitumor effects. The present invention thus features methods of preventing and treating cancer by administration of eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate), followed by one or more other agents [e.g., capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based antineoplastic agent (e.g., carboplatin, cisplatin, or oxaliplatin), doxorubicin, or ixabepilone].

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.

In an embodiment, the disclosure provides methods for treating a subject (e.g., a human patient) having or at risk of developing breast cancer (e.g., a subject diagnosed with breast cancer, in treatment for breast cancer, or in post-therapy recovery from breast cancer). The methods involve administering to the subject (i) eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) and, subsequently, (ii) a second agent selected from the group consisting of capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based anti-neoplastic agent (e.g., cisplatin, carboplatin, or oxaliplatin), doxorubicin, and ixabepilone. The treatment can optionally be carried out as neoadjuvant treatment prior to, e.g., surgery. In various examples, the breast cancer is a primary tumor, locally advanced, metastatic, and/or characterized as estrogen receptor positive or negative, progesterone receptor positive or negative, HER-2 positive or negative, or triple-negative breast cancer.

In certain embodiments, the eribulin or the pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) is administered by intravenous infusion (e.g., for about 1 to about 20 minutes, or about 2 to about 5 minutes), in an amount in the range of about 0.1 mg/m² to about 20 mg/m² (e.g., about 1.1 mg/m² or 1.4 mg/m²), and/or once on each of days 1 and 8 of a 21-day cycle.

In various embodiments, the eribulin or the pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) is completed prior to administration of the second agent, while in other embodiments, administration of the eribulin or the pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) continues after administration of the second agent begins.

In certain embodiments, the second agent administered is capecitabine, which can, for example, be administered daily for two weeks, followed by a one-week rest.

In various embodiments, treatment according to the methods as defined above: (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.

In another embodiment, the disclosure also includes methods for decreasing the size of a tumor in a subject having breast cancer. These methods include administering to the subject (i) eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) and, subsequently, (ii) a second agent selected from the group consisting of capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based anti-neoplastic agent (e.g., cisplatin, carboplatin, or oxaliplatin), doxorubin, and ixabepilone. The eribulin or pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) and/or other agent can be administered, optionally, as described above and elsewhere herein, and can result in, e.g., one or more of the effects listed above (i-x). This treatment can optionally be carried out in the neoadjuvant context prior to, e.g., surgery. In various examples, the breast cancer is a primary tumor, locally advanced, metastatic, and/or characterized as estrogen receptor positive or negative, progesterone receptor positive or negative, HER-2 positive or negative, or triple-negative breast cancer.

In a further embodiment, the disclosure includes methods for increasing the efficacy of an agent selected from the group consisting of capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based anti-neoplastic agent (e.g., cisplatin, carboplatin, or oxaliplatin), doxorubin, and ixabepilone in treating breast cancer in a subject. These methods involve administering eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) to the subject prior to the agent. In various examples, the eribulin or pharmaceutically acceptable salt thereof (e.g., eribulin mesylate) and/or other agent are administered in schedules and doses, as well as to particular subjects, as described above and elsewhere herein (to achieve, e.g., one or more of the effects listed above).

In an additional embodiment, the disclosure includes kits for use in treating breast cancer or decreasing tumor size in a subject having breast cancer. The kits include (i) eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate), and (ii) a second agent selected from the group consisting of capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based anti-neoplastic agent (e.g., cisplatin, carboplatin, or oxaliplatin), doxorubin, and ixabepilone, optionally in dosage form. Optionally, the kits include instructions for use and/or devices or reagents for administration.

The disclosure also includes the use of eribulin, or a pharmaceutically-acceptable salt thereof (e.g., eribulin mesylate), and a subsequently administered second agent, as described herein, for treating a subject having or at risk of developing breast cancer, as described herein, or for preparing a medicament for use in this purpose.

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 or at risk of developing breast cancer, the use further comprising a second agent to be subsequently administered to the subject, wherein the second agent is selected from the group consisting of capecitabine, an anti-mitotic agent, a platinum-based anti-neoplastic agent, doxorubin, and ixabepilone.

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 the second agent is selected from the group consisting of capecitabine, an anti-mitotic agent, a platinum-based anti-neoplastic agent, doxorubin, and ixabepilone.

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 selected from the group consisting of capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based anti-neoplastic agent (e.g., cisplatin, carboplatin, or oxaliplatin), doxorubin, and ixabepilone in treating breast cancer in a subject, the use comprising eribulin or a pharmaceutically acceptable salt thereof to be administered to the subject prior to said agent.

In another aspect, there is provided a kit for use in treating breast cancer or decreasing tumor size in a subject having breast cancer, the kit comprising (i) eribulin or a pharmaceutically acceptable salt thereof, and (ii) a second agent selected from the group consisting of capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based anti-neoplastic agent (e.g., cisplatin, carboplatin, or oxaliplatin), doxorubin, and ixabepilone, optionally in dosage form.

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.,
5 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
10 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
15 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 or at risk of developing breast cancer, the use further comprising a second agent to be subsequently administered to the subject, wherein the second agent is selected from the group consisting of capecitabine, an anti-mitotic agent, a platinum-based anti-neoplastic agent, doxorubin, and ixabepilone.
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 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 method 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 about 1 to about 20 minutes.
12. The use of claim 11, wherein said intravenous infusion is for about 2 to about 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 about 0.1 mg/m² to about 20 mg/m².

14. The 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/m² or 1.4 mg/m².

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 an anti-mitotic agent.

21. The use of claim 20, wherein said anti-mitotic agent is paclitaxel or docetaxel.

22. The use of claim 1, wherein said second agent is a platinum-based anti-neoplastic agent.

23. The use of claim 22, wherein said platinum-based anti-neoplastic agent is selected from the group consisting of cisplatin, carboplatin, and oxaliplatin.

24. The use of claim 1, wherein said second agent is doxorubicin.

25. The use of claim 1, wherein said second agent is ixabepilone.

26. 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.

27. 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.

28. 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 the second agent is selected from the group consisting of capecitabine, an anti-mitotic agent, a platinum-based anti-neoplastic agent, doxorubin, and ixabepilone.

29. Use of eribulin or a pharmaceutically acceptable salt thereof the manufacture of a medicament for increasing the efficacy of an agent selected from the group consisting of capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based anti-neoplastic agent (e.g., cisplatin, carboplatin, or oxaliplatin), doxorubin, and ixabepilone in treating breast cancer in a subject, the use comprising eribulin or a pharmaceutically acceptable salt thereof to be administered to the subject prior to said agent.

30. A kit for use in treating breast cancer or decreasing tumor size in a subject having breast cancer, the kit comprising (i) eribulin or a pharmaceutically acceptable salt thereof, and (ii) a second agent selected from the group consisting of capecitabine, an anti-mitotic agent (e.g., paclitaxel or docetaxel), a platinum-based anti-neoplastic agent (e.g., cisplatin, carboplatin, or oxaliplatin), doxorubin, and ixabepilone, optionally in dosage form.