

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 (i) 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, and ixabepilone, or (ii) consisting of doxorubicin as the sole additional agent to be subsequently administered to the subject.

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 (i) 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, and ixabepilone, or (ii) consisting of doxorubicin as the sole additional agent to be subsequently administered to the subject.

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, a platinum-based anti-neoplastic agent, doxorubicin, 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.

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.

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 (i) 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, and ixabepilone, or (ii) consisting of doxorubicin as the sole additional agent to be subsequently administered to the 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 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 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 (i) 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, and ixabepilone, or (ii) consisting of doxorubicin as the sole additional agent to be subsequently administered to the subject.

29. Use of eribulin or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for increasing the efficacy of an agent selected from the group consisting of capecitabine, an anti-mitotic agent, a platinum-based anti-neoplastic agent, doxorubicin, 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. The use according to claim 29, wherein the anti-mitotic agent is paclitaxel or docetaxel, or the platinum-based anti-neoplastic agent is cisplatin, carboplatin, or oxaliplatin.

31. 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.

32. The use of claim 1, wherein eribulin is to be administered 1, 2, 3, 4, 5, or 6 days or 1-12 weeks before the second agent.