DM1 (T- DM1) and pertuzumab have individually demonstrated activity in MBC patients, and a combination of pertuzumab and trastuzumab has been shown to be active in HER-positive MBC patients (Baselga J, et al. "A Phase II trial of trastuzumab and pertuzumab in patients with HER2 -positive metastatic breast cancer that had progressed during trastuzumab therapy: full response data", European Society of Medical Oncology, Stockholm, Sweden, September 12-16, 2008).

[0013] SUMMARY

[0014] The disclosure relates generally to the anti-HER2 antibody-drug conjugate, trastuzumab-MCC-DM1, administered in combination with one or more chemotherapeutic agents to inhibit the growth of cancer cells. Certain combinations of trastuzumab-MCC-DM1 and a chemotherapeutic agent show synergistic effects in inhibiting the growth of cancer cells in vitro and in vivo. The combinations and methods of the disclosure may be useful in the treatment of hyperproliferative disorders such as cancer. The combinations may inhibit tumor growth in mammals and may be useful for treating human cancer patients.

[0015] Disclosed is a method for the treatment of a hyperproliferative disorder comprising administering a therapeutic combination as a combined formulation or by alternation to a mammal, wherein the therapeutic combination comprises a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of a chemotherapeutic agent selected from a HER2 dimerization inhibitor antibody, an anti-VEGF antibody, 5-FU, carboplatin, lapatinib, ABT-869, docetaxel, GDC-0941, and GNE-390.

[0016] The therapeutically effective amount of trastuzumab-MCC-DM1 and the therapeutically effective amount of the chemotherapeutic agent may be administered as a combined formulation or by alternation.

[0017] The disclosure also relates to methods of using the compositions for *in vitro, in situ,* and *in vivo* diagnosis or treatment of mammalian cells, organisms, or associated pathological conditions.

[0018] The disclosure also relates to methods wherein administration of the therapeutic combination results in a synergistic effect.

[0019] Disclosed are pharmaceutical compositions comprising trastuzumab-MCC-DM1, a chemotherapeutic agent selected from a HER2 dimerization inhibitor antibody, an anti-VEGF antibody, 5-FU, carboplatin, lapatinib, ABT-869, docetaxel, GDC-0941, and GNE-390; and one or more pharmaceutically acceptable carrier, glidant,

diluent, or excipient.

[0019a] In one aspect, there is provided a pharmaceutical composition comprising trastuzumab-MCC-DM1, a chemotherapeutic agent selected from GDC-0941 and GNE-390; and one or more pharmaceutically acceptable carrier, glidant, diluent, or excipient.

[0020] Disclosed are methods of treating a hyperproliferative disease or disorder, comprising administering to a mammal in need of such treatment effective amounts of trastuzumab-MCC-DM1 and a chemotherapeutic agent.

Trastuzumab-MCC-DM1 and the chemotherapeutic agent may be co-formulated for administration in a combination as a pharmaceutical formulation or they may be administered separately in alternation (alternating, sequential dosages) as a therapeutic combination. In one embodiment, T-DM1 is delivered by infusion and the chemotherapeutic agent is delivered orally.

[0021] Disclosed are methods to predict effective drug combinations for in vivo efficacy where the combinations include trastuzumab-MCC-DM1 and an anti cancer, standard-of-care, chemotherapeutic agent. Efficacy data from in vitro cell proliferation and in vivo tumor xenograft experiments are analyzed qualitatively and quantitatively. Quantitative analysis methods may be based on the Chou & Talalay median effect and isobolograms generating a combination index (CI) value to denote synergy, antagonism, or additivity, or on the Bliss Independence ribbon graph deflection.

[0022] Disclosed is a method of using a therapeutic combination of the disclosure to treat a disease or condition such as cancer, including one modulated by HER2 or KDR9 (VEGF receptor 1) in a mammal.

[0023] Disclosed is the use of a therapeutic combination of the disclosure in the preparation of a medicament for the treatment of a disease or condition such as cancer, including one modulated by HER2 or KDR9 (VEGF receptor 1) in a mammal.

[0023a] In another aspect, there is provided a therapeutic combination for use in the treatment of cancer expressing ErbB2, wherein the treatment comprises administration of a therapeutic combination as a combined formulation or by alternation to a mammal, wherein the therapeutic combination comprises a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of a chemotherapeutic agent selected from GDC-0941 and GNE-390.

[0023b] In another aspect, there is provided use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for the treatment of cancer expressing ErbB2, wherein the pharmaceutical composition is to be administered as a combined formulation or by alternation to a mammal, wherein the pharmaceutical composition comprises a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of a chemotherapeutic agent selected from GDC-0941 and GNE-390.

[0023c] In another aspect, there is provided use of a therapeutic combination in the manufacture of a medicament for the treatment of breast cancer expressing ErbB2, wherein the therapeutic combination is to be administered to a mammal as a combined formulation or by alternation, and comprises a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of a chemotherapeutic agent selected from GDC-0941 and GNE-390.

[0024] Disclosed are articles of manufacture or kits comprising trastuzumab-MCC-DM1, a chemotherapeutic agent, a container, and optionally a package insert or label indicating a treatment.

[0025] Disclosed is a method for determining compounds to be used in combination for the treatment of cancer comprising: a) administering a therapeutic combination of trastuzumab-MCC-DM1, and a chemotherapeutic agent selected from a HER2 dimerization inhibitor antibody, an anti-VEGF antibody, 5-FU, carboplatin, lapatinib, ABT-869, docetaxel, GDC-0941, and GNE-390 to an in vitro tumor cell line, and b) measuring a synergistic or non-synergistic effect.

[0026] Additional advantages and novel features of this disclosure shall be set forth in part in the description that follows, and in part will become apparent to those skilled in the art upon examination of the following specification or may be learned by the practice of the

disclosure. The advantages of the disclosure may be realized and attained by means of the instrumentalities, combinations, compositions, and methods particularly pointed out in the appended claims.

[0027] BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Figure 1 shows a plot of SK-BR-3 in vitro cell viability at 3 days versus IC50 multiple concentrations of trastuzumab, trastuzumab-MCC-DM1 (T-DM1), and the combination of trastuzumab and T-DM1.

[0029] Figure 2 shows a plot of BT-474 EEI in vitro cell viability at 3 days versus IC50 multiple concentrations of trastuzumab, trastuzumab-MCC-DM1 (T-DM1), and the combination of trastuzumab and T-DM1.

[0030] Figure 3 shows a plot of MDA-MB- 175 in vitro cell viability at 5 days versus IC50 multiple concentrations of pertuzumab, trastuzumab-MCC-DM1 (T-DM1), and the combination of pertuzumab and T-DM1.

[0031] Figure 3 a shows a plot of MDA-MB- 175 in vitro cell viability at 5 days versus IC50 multiple concentrations of pertuzumab, trastuzumab-MCC-DM1 (T-DM1), and the combination of pertuzumab and T-DM1.

[0032] Figure 4 shows a plot of BT-474 in vitro cell viability at 5 days versus various fixed doses of pertuzumab in combination with dose response of trastuzumab-MCC-DM1 (T-DM1), and various doses of T-DM1 alone.

[0033] Figure 5 shows a plot of BT-474 in vitro cell viability at 5 days versus various fixed doses of trastuzumab-MCC-DM1 (T-DM1) in combination with dose response of pertuzumab, and various doses of pertuzumab alone.

[0034] Figure 6 shows a plot of BT-474 in vitro cell viability at 5 days versus IC50 multiple concentrations of pertuzumab, trastuzumab-MCC-DM1 (T-DM1), and the combination of pertuzumab and T-DM1.

[0035] Figure 7 shows a plot of SK-BR-3 in vitro cell viability at 3 days versus varying doses of T-DM1 in combination with fixed doses of lapatinib (4.5 nM, 14 nM, 41 nM, 123 nM), and varying doses of T-DM1 alone (0-1000 ng/ml).

[0036] Figure 7a shows a plot of SK-BR-3 in vitro cell viability at 3 days versus T-DM1, lapatinib, and fixed dose ratio combinations of T-DM1 and lapatinib.

[0037] Figure 8a shows a plot of BT-474 in vitro cell viability at 3 days versus T-DM1, lapatinib, and fixed dose ratio combinations of T-DM1 and lapatinib.

[0038] Figure 8 shows a plot of BT-474 in vitro cell viability at 3 days versus varying

Claims

1. A therapeutic combination for use in the treatment of cancer expressing ErbB2, wherein the treatment comprises administration of a therapeutic combination as a combined formulation or by alternation to a mammal, wherein the therapeutic combination comprises a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of a chemotherapeutic agent selected from GDC-0941 and GNE-390.

2. A therapeutic combination for use according to claim 1, wherein the chemotherapeutic agent is GNE-390.

3. A therapeutic combination for use according to claim 1, wherein the chemotherapeutic agent is GDC-0941.

4. A therapeutic combination for use according to any one of the preceding claims, wherein the therapeutically effective amount of trastuzumab-MCC-DM1 and the therapeutically effective amount of the chemotherapeutic agent are to be administered as a combined formulation.

5. A therapeutic combination for use according to any one of claims 1 to 3, wherein the therapeutically effective amount of trastuzumab-MCC-DM1 and the therapeutically effective amount of the chemotherapeutic agent are to be administered by alternation.

6. A therapeutic combination for use according to claim 5 wherein the mammal is to be administered the chemotherapeutic agent and then subsequently to be administered trastuzumab-MCC-DM1.

7. A therapeutic combination for use according to any one of the preceding claims, wherein the therapeutic combination is to be administered at three week intervals to a human with the hyperproliferative disorder.

8. A therapeutic combination for use according to any one of claims 1 to 6, wherein trastuzumab-MCC-DM1 is to be administered at intervals from one week to three weeks to a human with the hyperproliferative disorder.

9. A therapeutic combination for use according to any one of the preceding claims, wherein the trastuzumab-MCC-DM1 is to be administered no more frequently than every 3 weeks at a dose of 2.4, 3.0 or 3.6 mg/kg intravenously.

10. A therapeutic combination for use according to any one of the preceding claims, wherein the amount of trastuzumab-MCC-DM and the amount of chemotherapeutic agent are each from 1 mg to 1000 mg and the amount of trastuzumab-MCC-DM1 and the amount of chemotherapeutic agent are in a ratio of 1:10 to 10:1 by weight.

11. A therapeutic combination for use according to any one of the preceding claims, wherein the mammal is a HER2 positive patient.

12. A therapeutic combination for use according to any one of the preceding claims, wherein the HER2 positive patient has received trastuzumab or lapatinib therapy.

13. A pharmaceutical composition comprising trastuzumab-MCC-DM1, a chemotherapeutic agent selected from GDC-0941 and GNE-390; and one or more pharmaceutically acceptable carrier, glidant, diluent, or excipient.

14. The pharmaceutical composition of claim 13 comprising a pharmaceutically acceptable glidant selected from silicon dioxide, powdered cellulose, microcrystalline cellulose, metallic stearates, sodium aluminosilicate, sodium benzoate, calcium carbonate, calcium silicate, corn starch, magnesium carbonate, asbestos free talc, stearowet C, starch, starch 1500, magnesium lauryl sulfate, magnesium oxide, and combinations thereof.

15. Use of the pharmaceutical composition of claim 13 in the manufacture of a medicament for the treatment of cancer expressing ErbB2, wherein the pharmaceutical composition is to be administered as a combined formulation or by alternation to a mammal, wherein the pharmaceutical composition comprises a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of a chemotherapeutic agent selected from GDC-0941 and GNE-390.

16. The use of claim 15, wherein the chemotherapeutic agent is GNE-390.

17. The use of claim 15, wherein the chemotherapeutic agent is GDC-0941.

18. The use of any one of claims 15 to 17, wherein the therapeutically effective amount of trastuzumab-MCC-DM1 and the therapeutically effective amount of the chemotherapeutic agent are to be administered as a combined formulation.

19. The use of any one of claims 15 to 17, wherein the therapeutically effective amount of trastuzumab-MCC-DM1 and the therapeutically effective amount of the chemotherapeutic agent are to be administered by alternation.

20. The use of claim 19 wherein the mammal is to be administered the chemotherapeutic agent and then subsequently to be administered trastuzumab-MCC-DM1.

21. The use of any one of claims 15 to 20, wherein the medicament is to be administered at three week intervals to a human with the hyperproliferative disorder.

22. The use of any one of claims 15 to 20, wherein trastuzumab-MCC-DM1 is to be administered at intervals from one week to three weeks to a human with the hyperproliferative disorder.

23. The use of any one of claims 15 to 22, wherein the trastuzumab-MCC-DM1 is to be administered no more frequently than every 3 weeks at a dose of 2.4, 3.0 or 3.6 mg/kg intravenously.

24. The use of any one of claims 15 to 23, wherein the amount of trastuzumab-MCC-DM and the amount of chemotherapeutic agent are each from 1 mg to 1000 mg and the amount of trastuzumab-MCC-DM1 and the amount of chemotherapeutic agent are in a ratio of 1:10 to 10:1 by weight.

25. The use of any one of claims 15 to 24, wherein the mammal is a HER2 positive patient.

26. The use of any one of claims 15 to 25, wherein the HER2 positive patient has received trastuzumab or lapatinib therapy.

27. Use of a therapeutic combination in the manufacture of a medicament for the treatment of breast cancer expressing ErbB2, wherein the therapeutic combination is to be administered to a mammal as a combined formulation or by alternation, and comprises a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of a chemotherapeutic agent selected from GDC-0941 and GNE-390.

28. The use of claim 27, wherein the therapeutic combination consists of a therapeutically effective amount of trastuzumab-MCC-DM1, and a therapeutically effective amount of a chemotherapeutic agent selected from GDC-0941 and GNE-390.

29. The use of claim 27, wherein the therapeutic combination does not comprise pertuzumab.

30. The use of any one of claims 27 to 29, wherein the chemotherapeutic agent is GNE-390.

31. The use of any one claims 27 to 30, wherein the chemotherapeutic agent is GDC-0941.

32. The use of any one of claims 27 to 31, wherein the therapeutically effective amount of trastuzumab-MCC-DM1 and the therapeutically effective amount of the chemotherapeutic agent are to be administered as a combined formulation.

33. The use of any one of claims 27 to 31, wherein the therapeutically effective amount of trastuzumab-MCC-DM1 and the therapeutically effective amount of the chemotherapeutic agent are to be administered by alternation.

34. The use of claim 33 wherein the mammal is to be administered the chemotherapeutic agent and then subsequently administered trastuzumab-MCC-DM1.

35. The use of claim 32, wherein the therapeutic combination is to be administered at about three week intervals to a human with the hyperproliferative disorder.

36. The use of any one of claims 27 to 35, wherein trastuzumab-MCC-DM1 is to be administered at intervals from about one week to three weeks to a human with the hyperproliferative disorder.

37. The use of claim 36, wherein the trastuzumab-MCC-DM1 is to be administered no more frequently than every 3 weeks at a dose of 2.4, 3.0 or 3.6 mg/kg intravenously.

38. The use of any one of claims 27 to 37, wherein the amount of trastuzumab-MCC-DM1 and the amount of chemotherapeutic agent are each from about 1 mg to about 1000 mg and the amount of trastuzumab-MCC-DM1 and the amount of chemotherapeutic agent are in a ratio of about 1:10 to about 10:1 by weight.

39. The use of any one of claims 27 to 38, wherein the hyperproliferative disorder is cancer expressing ErbB2.

40. The use of any one of claims 27 to 39, wherein the mammal is a HER2 positive patient.

41. The use of any one of claims 27 to 40, wherein the HER2 positive patient has received trastuzumab or lapatinib therapy.