

TREATMENT OF CANCER WITH HER2XCD3 BISPECIFIC ANTIBODIES IN COMBINATION WITH ANTI-HER2MAB

SEQUENCE LISTING

5 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 4, 2020, is named 50474-197WO2_Sequence_Listing_3.4.20_ST25 and is 8,354 bytes in size.

FIELD OF THE INVENTION

10 The present invention relates to the treatment of HER2-positive cancers using HER2 antibodies, such as a combination of a HER2 T cell-dependent bispecific antibody (HER2 TDB) with another HER2 antibody.

BACKGROUND

15 Cancers are characterized by the uncontrolled growth of cell subpopulations. Cancers are the leading cause of death in the developed world and the second leading cause of death in developing countries, with over 14 million new cancer cases diagnosed and over eight million cancer deaths occurring each year. According to the American Cancer Society, an estimated 1,762,450 new cases of cancer and 606,880 deaths from cancer will occur in the United States in 2019. As the elderly population
20 has grown, the incidence of cancer has concurrently risen, as the probability of developing cancer is more than two-fold higher after the age of seventy. Cancer care thus represents a significant and ever-increasing societal burden.

 Human epidermal growth factor receptor 2 (HER2)-positive cancers, such as breast cancer and gastric cancer, represent some of the most common cancers in the world. Locally advanced and
25 metastatic HER2-positive breast and gastric cancers largely remain incurable diseases, with most patients progressing after receiving HER2-targeted therapies. While important advances have been achieved with the introduction of new anti-cancer agents, overall survival has been only marginally improved, and the long-term prognosis of patients with HER2-positive cancers who experience disease
 progression during or following a first-line treatment regimen remains dismal.

30 Thus, there is an unmet need in the field for the development of safe and efficacious treatment regimens for the treatment of HER2-positive cancers.

SUMMARY

 The present disclosure relates to methods of treating a subject having a HER2-positive cancer
35 using HER2-targeted T cell-dependent bispecific (TDB) antibodies.

 In one example, the disclosure provides a method of treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, the method comprising administering to the subject a treatment regimen comprising a HER2 antibody (e.g., a HER2 antibody that is not a HER2 T cell-
40 dependent antibody (TDB), such as a monospecific HER2 antibody, e.g., a monospecific, bivalent HER2 antibody, e.g., trastuzumab) and a HER2 TDB comprising an anti-HER2 arm and an anti-CD3 arm (e.g., BTRC4017A), wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, and wherein

the treatment regimen results in an increased therapeutic index of the HER2 TDB as compared to treatment with the HER2 TDB in the absence of the HER2 antibody. In some examples, the increased therapeutic index is associated with a decreased likelihood of experiencing an on-target/off-tumor effect as compared to treatment with the HER2 TDB in the absence of the HER2 antibody. In some examples, the on-target/off-tumor effect is a symptom of pulmonary toxicity (e.g., interstitial lung disease, acute respiratory distress syndrome, dyspnea, cough, fatigue, and pulmonary infiltrates), an elevated liver enzyme level, dry mouth, dry eyes, mucositis, esophagitis, or a urinary symptom. In some examples, the increased therapeutic index is associated with a decreased likelihood of experiencing an immunogenic side effect as compared to treatment with the HER2 TDB in the absence of the HER2 antibody. The immunogenic side effect may include, e.g., an elevated level of anti-drug antibodies, an infusion/administration-related reaction (ARR), cardiac dysfunction, a pulmonary reaction, or cytokine release syndrome (CRS).

In one aspect, the present disclosure refers to use of a HER2 antibody in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 T cell-dependent bispecific antibody (TDB), wherein the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, and wherein the use results in an increased therapeutic index of the HER2 TDB as compared to use of the HER2 TDB in the absence of the HER2 antibody.

In one aspect, the present disclosure refers to use of a HER2 TDB in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 antibody, wherein the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, and wherein the use results in an increased therapeutic index of the HER2 TDB as compared to use of the HER2 TDB in the absence of the HER2 antibody.

In some examples, the HER2 TDB and the HER2 antibody bind competitively to domain IV of HER2. In some examples, the HER2 antibody comprises: (i) a complementarity-determining region (CDR)-H1 comprising the amino acid sequence of SEQ ID NO: 1; (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2; (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3; (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4; (v) a CDR -L2 comprising the amino acid sequence of SEQ ID NO: 5; and (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6. In some examples, the HER2 antibody comprises a variable heavy chain domain (V_H) comprising at least 95% sequence identity (e.g., at least 96%, 97%, 98%, 99%, or 100% sequence identity) to the amino acid sequence of SEQ ID NO: 7 and/or a variable light chain domain (V_L) comprising at least 95% sequence identity (e.g., at least 96%, 97%, 98%, 99%, or 100% sequence identity) to the amino acid sequence of SEQ ID NO: 8. In particular examples, the V_H comprises the amino acid sequence of SEQ ID NO: 7 and/or the V_L comprises the amino acid sequence of SEQ ID NO: 8.

In some examples, the HER2 antibody (e.g., the additional HER2 antibody that is not a HER2 TDB) is monospecific and/or bivalent to HER2. In some examples, the HER2 antibody is a full-length antibody comprising an Fc region (e.g., trastuzumab). In some examples, the HER2 antibody is an Fc-modified trastuzumab variant, e.g., an Fc-modified trastuzumab variant having one or more amino acid modifications that reduces effector function (e.g., one or more substitution mutations, e.g., at amino acid residue L234, L235, and/or P329 (EU numbering). For example, in some examples, the one or more amino acid modifications comprise the substitution mutations L234A, L235A, and P329G (LALAPG).

In some examples of any of the preceding methods, the anti-HER2 arm of the HER2 TDB comprises a HER2 binding domain comprising: (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1; (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2; (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3; (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4; (v) a CDR -L2 comprising the amino acid sequence of SEQ ID NO: 5; and (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6. In some examples, the HER2 binding domain comprises a V_H comprising at least 95% sequence identity (e.g., at least 96%, 97%, 98%, 99%, or 100% sequence identity) to the amino acid sequence of SEQ ID NO: 7 and/or a V_L comprising at

least 95% sequence identity (e.g., at least 96%, 97%, 98%, 99%, or 100% sequence identity) to the amino acid sequence of SEQ ID NO: 8. In some examples, the V_H of the HER2 binding domain comprises the amino acid sequence of SEQ ID NO: 7 and/or the V_L of the HER2 binding domain comprises the amino acid sequence of SEQ ID NO: 8.

5 In some examples, the anti-CD3 arm of the HER2 TDB comprises a CD3 binding domain comprising: (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 9; (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 10; (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 11; (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12; (v) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13; and (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14. In some examples, the CD3 binding domain comprises a V_H comprising at least 95% sequence identity (e.g., at least 96%, 97%, 98%, 99%, or 100% sequence identity) to the amino acid sequence of SEQ ID NO: 15 and/or a variable V_L comprising at least 95% sequence identity (e.g., at least 96%, 97%, 98%, 99%, or 100% sequence identity) to the amino acid sequence of SEQ ID NO: 16. In some examples, the V_H of the CD3 binding domain comprises the amino acid sequence of SEQ ID NO: 15 and/or the V_L of the CD3 binding domain comprises the amino acid sequence of SEQ ID NO: 16.

In one aspect, the present disclosure refers to use of a HER2 antibody in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 TDB, wherein (a) the HER2 antibody is trastuzumab or an Fc-modified trastuzumab variant, and (b) the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the anti-HER2 arm comprises a HER2 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4;
- (v) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 5; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and

wherein the anti-CD3 arm comprises a CD3 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 9;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 10;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 11;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12;
- (v) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14;

wherein the use results in an increased therapeutic index of the HER2 TDB as compared to use of the HER2 TDB in the absence of the HER2 antibody.

In one aspect, the present disclosure refers to use of a HER2 TDB in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 antibody, wherein (a) the HER2 antibody is trastuzumab or an Fc-modified trastuzumab variant,

and (b) the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the anti-HER2 arm comprises a HER2 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4;
- (v) a CDR -L2 comprising the amino acid sequence of SEQ ID NO: 5; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and

wherein the anti-CD3 arm comprises a CD3 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 9;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 10;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 11;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12;
- (v) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14;

wherein the use results in an increased therapeutic index of the HER2 TDB as compared to use of the HER2 TDB in the absence of the HER2 antibody.

In some examples, (i) the anti-HER2 arm of the HER2 TDB comprises a HER2 binding domain comprising (a) a V_H comprising an amino acid sequence of SEQ ID NO: 7 and (b) a V_L comprising an amino acid sequence of SEQ ID NO: 8, and (ii) the anti-CD3 arm of the HER2 TDB comprises a CD3 binding domain comprising (a) a V_H comprising an amino acid sequence of SEQ ID NO: 15 and (b) a V_L comprising an amino acid sequence of SEQ ID NO: 16. In some examples, the HER2 TDB is BTRC4017A.

In some examples of any of the methods described herein, the HER2 TDB is a full-length antibody comprising a modified Fc region. The modified Fc region can include one or more substitution mutations that reduces effector function of the HER2 TDB. In some examples, the one or more substitution mutations comprise mutations at amino acid residues L234, L235, and/or D265 (EU numbering). In some examples, the one or more substitution mutations are L234A, L235A, and D265A. Additionally or alternatively, the one or more substitution mutations comprise an aglycosylation site mutation (e.g., an aglycosylation site mutation at amino acid residue N297 (EU numbering), e.g., an aglycosylation site mutation of N297G or N297A. In some examples, the modified Fc region comprises N297G, L234A, L235A, and D265A substitution mutations. In some examples, the HER2 TDB comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 ($CH1_1$) domain, a first CH2 ($CH2_1$) domain, a first CH3 ($CH3_1$) domain, a second CH1 ($CH1_2$) domain, second CH2 ($CH2_2$) domain, and a second CH3 ($CH3_2$) domain. In some examples, at least one of the one or more heavy chain constant domains is paired with another heavy chain constant domain, wherein: (i) the $CH3_1$ and $CH3_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH3_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH3_2$ domain; or (ii) the $CH2_1$ and $CH2_2$ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the $CH2_1$ domain is positionable in the cavity or protuberance, respectively, in the $CH2_2$ domain.

In another example, the disclosure provides a method of treating or delaying the progression of a HER2-positive cancer (e.g., a HER2-positive breast cancer or a HER2-positive gastric cancer) in a subject in need thereof, the method comprising administering to the subject a treatment regimen comprising a HER2 antibody and a HER2 TDB, wherein (a) the HER2 antibody is trastuzumab or an Fc-modified trastuzumab variant, and (b) the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the anti-HER2 arm comprises a HER2 binding domain comprising: (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1; (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2; (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3; (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4; (v) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 5; and (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and wherein the anti-CD3 arm comprises a CD3 binding domain comprising: (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 9; (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 10; (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 11; (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12; (v) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13; and (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14; wherein the treatment regimen results in an increased therapeutic index of the HER2 TDB as compared to treatment with the HER2 TDB in the absence of the HER2 antibody. The increased therapeutic index may be associated with a decreased likelihood of experiencing an on-target/off-tumor effect as compared to treatment with the HER2 TDB in the absence of the HER2 antibody. In some examples, the on-target/off-tumor effect is a symptom of pulmonary toxicity (e.g., interstitial lung disease, acute respiratory distress syndrome, dyspnea, cough, fatigue, and pulmonary infiltrates), an elevated liver enzyme level, dry mouth, dry eyes, mucositis, esophagitis, or a urinary symptom. In some examples, the increased therapeutic index is associated with a decreased likelihood of experiencing an immunogenic side effect as compared to treatment with the HER2 TDB in the absence of the HER2 antibody. The immunogenic side effect may include, e.g., an elevated level of anti-drug antibodies, an infusion/administration-related reaction (ARR), cardiac dysfunction, a pulmonary reaction, or cytokine release syndrome (CRS).

In some examples of either of the aforementioned examples, the HER2 antibody is administered prior to administration of the HER2 TDB.

In some examples, the HER2 antibody is administered at a dose of about 5 mg/kg to about 10 mg/kg (e.g., 5 mg/kg to 10 mg/kg or 6 mg/kg to 8 mg/kg, e.g., about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, or about 10 mg/kg). In some examples, the HER2 antibody is administered about once every three weeks (Q3W).

In some examples, the HER2 TDB is administered at a fixed dose of 0.001 mg to 500 mg (e.g., from 0.003 mg to 250 mg, from 0.005 mg to 200 mg, from 0.01 mg to 150 mg, from 0.05 mg to 120 mg, from 0.1 mg to 100 mg, from 0.5 mg to 80 mg, or from 1.0 mg to 50 mg, e.g., from 0.001 mg to 0.005 mg, from 0.005 mg to 0.01 mg, from 0.01 mg to 0.05 mg, from 0.05 mg to 0.1 mg, from 0.1 mg to 0.5 mg, from 0.5 mg to 1.0 mg, from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, from 90 mg to 100 mg, from 100 mg to 120 mg, from 120 mg to 150 mg, from 150 mg to 200 mg, from 200 mg to 250 mg, from 250 mg to 300 mg, from 300 mg to 350 mg, from

350 mg to 400 mg, from 400 mg to 450 mg, or from 450 mg to 500 mg, e.g., about 0.003 mg, about 0.005 mg, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 150 mg, about 200 mg, or about 250 mg, e.g., 0.003 mg, 0.009 mg, 0.027 mg, 0.081 mg, 0.24 mg, 0.72 mg, 1.08 mg, 1.51 mg, 2.2 mg, 2.3 mg, 4.0 mg, 4.6 mg, 6.6 mg, 8.0 mg, 9.2 mg, 12 mg, 13.2 mg, 14.8 mg, 18.4 mg, 19.8 mg, 26.4 mg, 36.8 mg, 51.5 mg, 52.8 mg, 61.3 mg, 72.1 mg, 105.6 mg, 147.8 mg, 176 mg, or 207 mg). In some examples, the HER2 TDB is administered about once every three weeks (Q3W).

In some examples of any of the methods described above, the treatment regimen comprises: (a) a first dose of the HER2 antibody; (b) a first dosing cycle (C1) after the first dose of the HER2 antibody, the C1 comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1; (c) a second dosing cycle (C2) after the C1, the C2 comprising: (i) a second dose of the HER2 antibody; and (ii) an additional dose of the HER2 TDB (C2D1) after the second dose of the HER2 antibody, wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1.

In another example of the disclosure, provided herein is a method of treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, the method comprising administering to the subject a treatment regimen comprising a HER2 antibody and a HER2 TDB, wherein the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, wherein the treatment regimen comprises: (a) a first dose of the HER2 antibody; (b) a first dosing cycle (C1) after the first dose of the HER2 antibody, the C1 comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1; (c) a second dosing cycle (C2) after the C1, the C2 comprising: (i) a second dose of the HER2 antibody; and (ii) an additional dose of the HER2 TDB (C2D1) after the second dose of the HER2 antibody, wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1.

In one aspect, the present disclosure refers to use of a HER2 antibody in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 TDB, wherein the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, wherein the use comprises:

- (a) a first dose of the HER2 antibody;
- (b) a first dosing cycle (C1) after the first dose of the HER2 antibody, the C1 comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1;
- (c) a second dosing cycle (C2) after the C1, the C2 comprising:
 - (i) a second dose of the HER2 antibody; and
 - (ii) an additional dose of the HER2 TDB (C2D1) after the second dose of the HER2 antibody, wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1.

In one aspect, the present disclosure refers to use of a HER2 TDB in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 antibody, wherein the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, wherein the use comprises:

- (a) a first dose of the HER2 antibody;
- (b) a first dosing cycle (C1) after the first dose of the HER2 antibody, the C1 comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1;
- (c) a second dosing cycle (C2) after the C1, the C2 comprising:
 - (i) a second dose of the HER2 antibody; and
 - (ii) an additional dose of the HER2 TDB (C2D1) after the second dose of the HER2 antibody, wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1.

5 In some examples, the first dose of the HER2 antibody is administered one day prior to the C1D1, and wherein the subject is monitored for a period of 30 minutes to 24 hours (e.g., 30 minutes to 2 hours, e.g., 30 minutes to 90 minutes, e.g., 30 minutes, 60 minutes, 90 minutes, or 120 minutes) between the first dose of the HER2 antibody and the C1D1.

10 In some examples, the first dose of the HER2 antibody is from 5 mg/kg to 10 mg/kg (e.g., about 6 mg/kg or about 8 mg/kg). In some examples, the first dose of the HER2 antibody is 6 mg/kg. In other examples, the first dose of the HER2 antibody is 8 mg/kg. In some examples, the second dose of the HER2 antibody is from 5 mg/kg to 10 mg/kg (e.g., about 6 mg/kg). In some examples, the second dose of the HER2 antibody is 6 mg/kg. In some examples, the first and/or second dose of the HER2 antibody is administered by infusion over a period of at least 30 minutes.

15 In some examples, the second dose of the HER2 antibody is administered on the same day as the C2D1. In some examples, the C1D2 is at least two-fold the dose of the C1D1 (e.g., at least

three-fold the dose of the C1D1). In some examples, the C1D1 is from 0.003 mg to 50 mg (e.g., from 0.003 mg to 50 mg, from 0.005 mg to 20 mg, from 0.01 mg to 10 mg, from 0.05 mg to 8 mg, or from 0.1 mg to 5 mg, e.g., from 0.001 mg to 0.005 mg, from 0.005 mg to 0.01 mg, from 0.01 mg to 0.05 mg, from 0.05 mg to 0.1 mg, from 0.1 mg to 0.5 mg, from 0.5 mg to 1.0 mg, from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, or from 40 mg to 50 mg, e.g., about 0.003 mg, about 0.005 mg, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg). In some examples, the C1D1 is 0.003 mg, 0.009 mg, 0.027 mg, 0.081 mg, 0.12 mg, 0.24 mg, 0.48 mg, 0.72 mg, 1.0 mg, 2.0 mg, 2.2 mg, 4.0 mg, 6.6 mg, 8.0 mg, 12 mg, 18 mg, 27 mg, or 40.5 mg.

In some examples, the C1D2 is from 0.009 mg to 200 mg (e.g., from 0.01 mg to 150 mg, from 0.05 mg to 100 mg, from 0.1 mg to 50 mg, from 0.5 mg to 20 mg, or from 1 mg to 10 mg, e.g., from 0.009 mg to 0.01 mg, from 0.01 mg to 0.05 mg, from 0.05 mg to 0.1 mg, from 0.1 mg to 0.5 mg, from 0.5 mg to 1.0 mg, from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, from 90 mg to 100 mg, from 100 mg to 120 mg, from 120 mg to 150 mg, or from 150 mg to 200 mg, e.g., about 0.009 mg, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 150 mg, or about 200 mg). In some examples, the C1D2 is 0.009 mg, 0.027 mg, 0.081 mg, 0.24 mg, 0.4 mg, 0.72 mg, 0.8 mg, 1.6 mg, 2.2 mg, 2.3 mg, 3.2 mg, 4.6 mg, 6.4 mg, 6.6 mg, 9.2 mg, 12.8 mg, 14.8 mg, 18.4 mg, 19.8 mg, 25.6 mg, 36.8 mg, 38.4, 51.5 mg, 57.6 mg, 72.1 mg, 86.4 mg, 61.3 mg, or 129.6 mg.

In some examples, e.g., in a one-step fractionation, the C2D1 and the C1D2 are equivalent.

In some examples, the C1 further comprises a third dose of the HER2 TDB (C1D3), wherein the C1D3 is greater than the C1D2. In some examples, the C1D1, the C1D2, and the C1D3 are cumulatively greater than a highest cleared dose of the HER2 TDB in a first dosing cycle of a one-step fractionation, dose-escalation dosing regimen (e.g., where the highest cleared dose is between about 0.01 mg and about 30 mg, e.g., from 0.5 mg to 25 mg, from 1 mg to 20 mg, or from 2 mg to 10 mg). In some examples, the C1D2 is from two-fold to ten-fold (e.g., about two-fold, about three-fold, about four-fold, about five-fold, about six-fold, about seven-fold, about eight-fold, about nine-fold, or about ten-fold) the dose of the C1D1. In some examples, the C1D3 is from two-fold to three-fold the dose of the C1D2. In some examples, the C2D1 and the C1D3 are equivalent.

In some examples, the C1D1 is from 0.01 mg to 20 mg (e.g., from 0.05 mg to 15 mg, from 0.1 mg to 10 mg, or from 0.5 mg to 5 mg, e.g., from 0.01 mg to 0.05 mg, from 0.05 mg to 0.1 mg, from 0.1 mg

to 0.5 mg, from 0.5 mg to 1.0 mg, from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 15 mg, or from 15 mg to 20 mg, e.g., about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, or about 20 mg).

In some examples, the C1D2 is from 0.1 mg to 100 mg (e.g., from 0.1 mg to 80 mg, from 0.5 mg to 50 mg, or from 1 mg to 10 mg, e.g., from 0.1 mg to 0.5 mg, from 0.5 mg to 1.0 mg, from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, or from 90 mg to 100 mg, e.g., about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg).

In some examples, the C1D3 is from 1 mg to 400 mg (e.g., from 10 mg to 300 mg, from 20 mg to 200 mg, or from 50 mg to 100 mg, e.g., from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, from 90 mg to 100 mg, from 100 mg to 120 mg, from 120 mg to 150 mg, from 150 mg to 200 mg, from 200 to 250 mg, from 250 mg to 300 mg, from 300 mg to 350 mg, or from 350 mg to 400 mg, e.g., about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg). In some examples, the C1D3 is 1.1 mg, 2.2 mg, 4.4 mg, 6.6 mg, 8.8 mg, 13.2 mg, 17.6 mg, 26.4 mg, 35.2 mg, 52.8 mg, 70.4 mg, 105.6 mg, 147.8 mg, 158.4 mg, 176 mg, 207 mg, 237.6 mg, or 356.4 mg.

In some examples, the method comprises administering to the subject the C1D1, the C1D2, and the C1D3 on or about Days 1, 8, and 15, respectively, of the C1. In some examples, the C1 is about 21 days. In some examples, the C2 is about 21 days.

In some examples, the method comprises administering to the subject the C2D1 on Day 1 of the C2. In some examples, the treatment regimen comprises one or more additional dosing cycles (e.g., up to 15 additional dosing cycles, e.g., one, two, three, four, five, six, seven eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen additional dosing cycles). In some examples, the length of each of the one or more additional dosing cycles is about 21 days. In some examples, each of the one or more additional dosing cycles comprises a single dose of the HER2 antibody and a single dose of the HER2 TDB (e.g., wherein the HER2 antibody is administered prior to the HER2 TDB on each of the additional dosing cycles, e.g., on Day 1 of each of the additional dosing cycles). In some examples,

the method comprises administering to the subject the HER2 antibody and the HER2 TDB on Day 1 of each of the one or more additional dosing cycles.

In another example, the disclosure provides a method of treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, the method comprising administering to the subject a treatment regimen comprising a HER2 TDB, wherein the treatment regimen comprises: (a) a first cycle (C1) comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1; and (b) a second cycle (C2) comprising an additional dose of the HER2 TDB (C2D1), wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1. In some examples, the C1D2 is at least two-fold the dose of the C1D1 (e.g., at least three-fold the dose of the C1D1).

In one aspect, the present disclosure refers to use of a HER2 TDB in the manufacture of a medicament for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein the use comprises:

(a) a first cycle (C1) comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1; and

(b) a second cycle (C2) comprising an additional dose of the HER2 TDB (C2D1), wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1.

In some examples, the C1D1 is from 0.003 mg to about 10 mg (e.g., from 0.005 mg to 9 mg, from 0.01 mg to 8 mg, from 0.05 mg to 7 mg, or from 0.1 mg to 5 mg, e.g., from 0.003 mg to 0.005 mg, from 0.005 mg to 0.01 mg, from 0.01 mg to 0.05 mg, from 0.05 mg to 0.1 mg, from 0.1 mg to 0.5 mg, from 0.5 mg to 1.0 mg, from 1.0 mg to 5 mg, or from 5 mg to 10 mg, e.g., about 0.003 mg, about 0.005 mg, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg).

In some examples, the C1D2 is from 0.009 to about 20 mg (e.g., from 0.01 mg to 15 mg, from 0.05 mg to 10 mg, or from 0.1 mg to 5 mg, e.g., from 0.009 mg to 0.01 mg, from 0.01 mg to 0.05 mg, from 0.05 mg to 0.1 mg, from 0.1 mg to 0.5 mg, from 0.5 mg to 1.0 mg, from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 15 mg, or from 15 mg to 20 mg, e.g., about 0.009 mg, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, or about 20 mg).

In some examples, the C2D1 and the C1D2 are equivalent. In other examples, the C1 further comprises a third dose of the HER2 TDB (C1D3) which is greater than the C1D2. In some examples, the C1D1, the C1D2, and the C1D3 are cumulatively greater than a highest cleared dose of the HER2 TDB in a first dosing cycle of a one-step fractionation, dose-escalation dosing regimen. In some examples, the highest cleared dose is between about 0.01 mg and about 30 mg. In some examples, the C1D2 is from two-fold to ten-fold the dose of the C1D1 (e.g., about three-fold, about four-fold, about five-fold, about six-fold, about seven-fold, about eight-fold, about nine-fold, or about ten-fold the dose of the C1D1). In some examples, the C1D3 is from two-fold to three-fold the dose of the C1D2. In some examples, the C2D1 and the C1D3 are equivalent.

In some examples, the C1D1 is from 0.01 mg to 20 mg (e.g., from 0.01 mg to 15 mg, from 0.05 mg to 10 mg, or from 0.1 mg to 5 mg, e.g., from 0.01 mg to 0.05 mg, from 0.05 mg to 0.1 mg, from 0.1 mg to 0.5 mg, from 0.5 mg to 1.0 mg, from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 15 mg, or from 15 mg to 20 mg, e.g., about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, or about 20 mg).

In some examples, the C1D2 is from 0.1 mg to 100 mg (e.g., from 0.1 mg to 80 mg, from 0.5 mg to 50 mg, or from 1 mg to 10 mg, e.g., from 0.1 mg to 0.5 mg, from 0.5 mg to 1.0 mg, from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, or from 90 mg to 100 mg, e.g., about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg).

In some examples, the C1D3 is from 1 mg to 200 mg (e.g., from 10 mg to 150 mg, from 20 mg to 120 mg, or from 50 mg to 100 mg, e.g., from 1.0 mg to 5 mg, from 5 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, from 90 mg to 100 mg, from 100 mg to 120 mg, from 120 mg to 150 mg, or from 150 mg to 200 mg, e.g., about 1.0 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 150 mg, or about 200 mg).

In some examples, the method comprises administering to the subject the C1D1, the C1D2, and the C1D3 on or about Days 1, 8, and 15, respectively, of the C1. In some examples, the C1 is about 21 days. Additionally or alternatively, in some examples, the C2 is 21 days. In some examples, the method comprises administering to the subject the C2D1 on Day 1 of the C2. The treatment regimen may include one or more additional dosing cycles (e.g., up to 15 additional dosing cycles, e.g., one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen additional dosing cycles). In some examples, each of the additional dosing cycles is about 21 days. In some examples, each of the additional dosing cycles comprises a single dose of the HER2 TDB. In some examples, the method comprises administering to the subject the HER2 TDB on Day 1 of each of the one or more additional dosing cycles. In some examples of any of the preceding examples, the HER2 antibody and/or the HER2 TDB are administered by intravenous infusion (e.g. by IV bag). In some examples, the treatment regimen results in an increased therapeutic index of the HER2 TDB as compared to a control treatment regimen (e.g., treatment with the HER2 TDB in the absence of the HER2 antibody, or a treatment regimen without fractionated dosing).

In some examples of any of the preceding example, the method further includes administering one or more additional therapeutic agents. For example, the one or more additional therapeutic agents can be tocilizumab, a corticosteroid, a PD-1 axis antagonist, or an antibody-drug conjugate. In some examples, the PD-1 axis binding antagonist is selected from the group consisting of a PD-L1 binding antagonist (e.g., MPDL3280A (atezolizumab), YW243.55.S70, MDX-1105, or MEDI4736), a PD-1 binding

antagonist (e.g., MDX-1106 (nivolumab), MK-3475 (pembrolizumab), and AMP-224), and a PD-L2 binding antagonist (e.g., a PD-L1 binding antibody or an immunoadhesin).

In some examples, the subject has been administered trastuzumab in a previous treatment regimen (e.g. as a treatment for a HER2-positive cancer).

In some examples, the HER2-positive cancer is a HER2-positive solid tumor. Additionally or alternatively, the HER2-positive cancer can be a locally advanced or metastatic HER2-positive cancer. In some examples, the HER2-positive cancer is a HER2-positive breast cancer or a HER2-positive gastric cancer (e.g., a HER2-positive gastroesophageal junction cancer or a HER2-positive colorectal cancer. In some examples, the HER2-positive cancer is selected from the group consisting of a HER2-positive gastroesophageal junction cancer, a HER2-positive colorectal cancer, a HER2-positive lung cancer (e.g., a HER2-positive non-small cell lung carcinoma), a HER2-positive pancreatic cancer, a HER2-positive colorectal cancer, a HER2-positive bladder cancer, a HER2-positive salivary duct cancer, a HER2-positive ovarian cancer (e.g., a HER2-positive epithelial ovarian cancer), or a HER2-positive endometrial cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a rendering of the crystal structure of the HER2 extracellular domain (ECD) bound by the HER2 binding domains 4D5 (trastuzumab), 2C4 (pertuzumab), and 7C2.

FIG. 2 is an immunoblot showing the relative expression of HER2 protein by MCF7 cells, HT55 cells, and KPL4 cells.

FIG. 3A is a graph showing relative killing of KPL4 cells by BTRC4017A alone (red circles); BTRC4017A + 230 µg/mL trastuzumab (blue squares); and BTRC4017A + 60 µg/mL trastuzumab (brown triangles) as a function of BTRC4017A concentration (ng/mL).

FIG. 3B is a graph showing relative killing of HT55 cells by BTRC4017A alone (red circles); BTRC4017A + 230 µg/mL trastuzumab (blue squares); and BTRC4017A + 60 µg/mL trastuzumab (brown triangles) as a function of BTRC4017A concentration (ng/mL). N.D. = Not determined.

FIG. 4 is a graph showing binding of trastuzumab (red circles) and trastuzumab-LALAPG (blue squares) to HER2-expressing SKBR3 cells as a function of concentration. Binding was detected using a goat anti-human-FITC secondary antibody, the presence of which was quantified by mean fluorescence intensity (MFI) using flow cytometry.

FIG. 5A is a trellis plot showing KPL4 tumor volume over the course of various treatments in a mouse model. The top row shows the effect of control treatments; the left-hand graph shows tumor growth in response to vehicle administration; the middle graph shows tumor growth in response to trastuzumab (HERCEPTIN®) without peripheral blood mononuclear cells (PBMCs); and the right-hand graph shows tumor growth in response to trastuzumab (HERCEPTIN®) with PBMCs. The middle row and bottom row show tumor growth over the course of treatment with BTRC4017A alone and in combination with trastuzumab (HERCEPTIN®), respectively. In the middle row and bottom row, the left-hand graph shows tumor growth in response to 0.05 mg/kg BTRC4017A; the middle graph shows tumor growth in response to 0.5 mg/kg BTRC4017A; and the right-hand graph shows tumor growth in response to 5.0 mg/kg BTRC4017A. Bold, solid lines represent the fitted tumor volume for each group. Dashed

WHAT IS CLAIMED IS:

1. Use of a HER2 antibody in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 T cell-dependent bispecific antibody (TDB), wherein the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, and wherein the use results in an increased therapeutic index of the HER2 TDB as compared to use of the HER2 TDB in the absence of the HER2 antibody.

2. Use of a HER2 TDB in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 antibody, wherein the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, and wherein the use results in an increased therapeutic index of the HER2 TDB as compared to use of the HER2 TDB in the absence of the HER2 antibody.

3. The use according to claim 1 or 2, wherein the increased therapeutic index is associated with a decreased likelihood of experiencing an on-target/off-tumor effect as compared to use of the HER2 TDB in the absence of the HER2 antibody.

4. The use according to claim 3, wherein the on-target/off-tumor effect is a symptom of pulmonary toxicity.

5. The use according to claim 4, wherein the symptom of pulmonary toxicity is selected from the group consisting of interstitial lung disease, acute respiratory distress syndrome, dyspnea, cough, fatigue, and pulmonary infiltrates.

6. The use according to claim 3, wherein the on-target/off tumor effect is selected from the group consisting of an elevated liver enzyme level, dry mouth, dry eyes, mucositis, esophagitis, and a urinary symptom.

7. The use according to any one of claims 1-6, wherein the increased therapeutic index is associated with a decreased likelihood of experiencing an immunogenic side effect as compared to use of the HER2 TDB in the absence of the HER2 antibody.

8. The use according to claim 7, wherein the immunogenic side effect is selected from the group consisting of an elevated level of anti-drug antibodies, an infusion/administration-related reaction (ARR), cardiac dysfunction, a pulmonary reaction, and cytokine release syndrome.

9. The use according to any one of claims 1-8, wherein the HER2 TDB and the HER2 antibody bind competitively to domain IV of HER2.

10. The use according to any one of claims 1-9, wherein the HER2 antibody comprises:

- (i) a complementarity-determining region (CDR)-H1 comprising the amino acid sequence of SEQ ID NO: 1;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4;
- (v) a CDR -L2 comprising the amino acid sequence of SEQ ID NO: 5; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6.

11. The use according to any one of claims 1-10, wherein the HER2 antibody comprises a variable heavy chain domain (V_H) comprising at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 7 and/or a variable light chain domain (V_L) comprising at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 8.

12. The use according to claim 11, wherein the V_H comprises the amino acid sequence of SEQ ID NO: 7 and/or the V_L comprises the amino acid sequence of SEQ ID NO: 8.

13. The use according to any one of claims 1-12, wherein the HER2 antibody is monospecific.

14. The use according to any one of claims 1-13, wherein the HER2 antibody is a full-length antibody comprising an Fc region.

15. The use according to any one of claims 1-14, wherein the HER2 antibody is trastuzumab.

16. The use according to any one of claims 1-14, wherein the HER2 antibody is an Fc-modified trastuzumab variant.

17. The use according to claim 16, wherein the Fc-modified trastuzumab variant comprises one or more amino acid modifications that reduces effector function.

18. The use according to claim 17, wherein the one or more amino acid modifications is a substitution mutation.

19. The use according to claim 18, wherein the substitution mutation is at amino acid residue L234, L235, and/or P329 (EU numbering).

20. The use according to claim 19, wherein the one or more amino acid modifications comprise the substitution mutations L234A, L235A, and P329G (LALAPG).

21. The use according to any one of claims 1-20, wherein the anti-HER2 arm of the HER2 TDB comprises a HER2 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4;
- (v) a CDR -L2 comprising the amino acid sequence of SEQ ID NO: 5; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6.

22. The use according to claim 21, wherein the HER2 binding domain comprises a V_H comprising at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 7 and/or a V_L comprising at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 8.

23. The use according to claim 22, wherein the V_H of the HER2 binding domain comprises the amino acid sequence of SEQ ID NO: 7 and/or the V_L of the HER2 binding domain comprises the amino acid sequence of SEQ ID NO: 8.

24. The use according to claim any one of claims 1-23, wherein the anti-CD3 arm of the HER2 TDB comprises a CD3 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 9;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 10;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 11;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12;
- (v) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14.

25. The use according to claim 24, wherein the CD3 binding domain comprises a V_H comprising at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 15 and/or a variable V_L comprising at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 16.

26. The use according to claim 25, wherein the V_H of the CD3 binding domain comprises the amino acid sequence of SEQ ID NO: 15 and/or the V_L of the CD3 binding domain comprises the amino acid sequence of SEQ ID NO: 16.

27. The use according to claim 26, wherein (i) the anti-HER2 arm of the HER2 TDB comprises a HER2 binding domain comprising (a) a V_H comprising an amino acid sequence of SEQ ID NO: 7 and (b) a V_L comprising an amino acid sequence of SEQ ID NO: 8, and (ii) the anti-CD3 arm of the HER2 TDB comprises a CD3 binding domain comprising (a) a V_H comprising an amino acid sequence of SEQ ID NO: 15 and (b) a V_L comprising an amino acid sequence of SEQ ID NO: 16.

28. The use according to any one of claims 1-27, wherein the HER2 TDB is a full-length antibody comprising a modified Fc region.

29. The use according to claim 28, wherein the modified Fc region comprises one or more substitution mutations that reduces effector function of the HER2 TDB.

30. The use according to claim 29, wherein the one or more substitution mutations comprise mutations at amino acid residues L234, L235, and/or D265 (EU numbering).

31. The use according to claim 30, wherein the one or more substitution mutations are L234A, L235A, and D265A.

32. The use according to claim 29, wherein the one or more substitution mutations comprise an aglycosylation site mutation.

33. The use according to claim 32, wherein the aglycosylation site mutation is at amino acid residue N297 (EU numbering).

34. The use according to claim 32, wherein the aglycosylation site mutation is N297G.

35. The use according to claim 32, wherein the aglycosylation site mutation is N297A.

36. The use according to any one of claims 28-34, wherein the modified Fc region comprises N297G, L234A, L235A, and D265A substitution mutations.

37. The use according to any one of claims 1-36, wherein the HER2 TDB comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 (CH1₁) domain, a first CH2 (CH2₁) domain, a first CH3 (CH3₁) domain, a second CH1 (CH1₂) domain, second CH2 (CH2₂) domain, and a second CH3 (CH3₂) domain.

38. The use according to claim 37, wherein at least one of the one or more heavy chain constant domains is paired with another heavy chain constant domain, wherein:

(i) the CH3₁ and CH3₂ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the CH3₁ domain is positionable in the cavity or protuberance, respectively, in the CH3₂ domain; or

(ii) the CH2₁ and CH2₂ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the CH2₁ domain is positionable in the cavity or protuberance, respectively, in the CH2₂ domain.

39. Use of a HER2 antibody in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said

medicament is to be administered in combination with a HER2 TDB, wherein (a) the HER2 antibody is trastuzumab or an Fc-modified trastuzumab variant, and (b) the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the anti-HER2 arm comprises a HER2 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4;
- (v) a CDR -L2 comprising the amino acid sequence of SEQ ID NO: 5; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and

wherein the anti-CD3 arm comprises a CD3 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 9;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 10;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 11;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12;
- (v) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14;

wherein the use results in an increased therapeutic index of the HER2 TDB as compared to use of the HER2 TDB in the absence of the HER2 antibody.

40. Use of a HER2 TDB in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 antibody, wherein (a) the HER2 antibody is trastuzumab or an Fc-modified trastuzumab variant, and (b) the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the anti-HER2 arm comprises a HER2 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4;
- (v) a CDR -L2 comprising the amino acid sequence of SEQ ID NO: 5; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and

wherein the anti-CD3 arm comprises a CD3 binding domain comprising:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 9;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 10;
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 11;
- (iv) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12;
- (v) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13; and
- (vi) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14;

wherein the use results in an increased therapeutic index of the HER2 TDB as compared to use of the HER2 TDB in the absence of the HER2 antibody.

41. The use according to any one of claims 1-40, wherein the HER2 antibody is to be administered prior to administration of the HER2 TDB.

42. The use according to any one of claims 1-41, wherein the HER2 antibody is to be administered at a dose of 5 mg/kg to 10 mg/kg.

43. The use according to any one of claims 1-42, wherein the HER2 antibody is to be administered about once every three weeks.

44. The use according to any one of claims 1-43, wherein the HER2 TDB is to be administered at a fixed dose of 0.001 mg to 500 mg.

45. The use according to any one of claims 1-44, wherein the HER2 TDB is to be administered about once every three weeks.

46. The use according to any one of claims 1-45, wherein the use comprises:

- (a) a first dose of the HER2 antibody;
- (b) a first dosing cycle (C1) after the first dose of the HER2 antibody, the C1 comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1;
- (c) a second dosing cycle (C2) after the C1, the C2 comprising:
 - (i) a second dose of the HER2 antibody; and
 - (ii) an additional dose of the HER2 TDB (C2D1) after the second dose of the HER2 antibody, wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1.

47. Use of a HER2 antibody in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said medicament is to be administered in combination with a HER2 TDB, wherein the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, wherein the use comprises:

- (a) a first dose of the HER2 antibody;
- (b) a first dosing cycle (C1) after the first dose of the HER2 antibody, the C1 comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1;
- (c) a second dosing cycle (C2) after the C1, the C2 comprising:
 - (i) a second dose of the HER2 antibody; and
 - (ii) an additional dose of the HER2 TDB (C2D1) after the second dose of the HER2 antibody, wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1.

48. Use of a HER2 TDB in the manufacture of a medicament for use in combinatorial therapy for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein said

medicament is to be administered in combination with a HER2 antibody, wherein the HER2 TDB comprises an anti-HER2 arm and an anti-CD3 arm, wherein the HER2 antibody and the HER2 TDB both bind domain IV of HER2, wherein the use comprises:

- (a) a first dose of the HER2 antibody;
- (b) a first dosing cycle (C1) after the first dose of the HER2 antibody, the C1 comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1;
- (c) a second dosing cycle (C2) after the C1, the C2 comprising:
 - (i) a second dose of the HER2 antibody; and
 - (ii) an additional dose of the HER2 TDB (C2D1) after the second dose of the HER2 antibody, wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1.

49. The use according to any one of claims 46-48, wherein the first dose of the HER2 antibody is to be administered one day prior to the C1D1, and wherein the subject is to be monitored for a period of 30 minutes to 24 hours between the first dose of the HER2 antibody and the C1D1.

50. The use according to any one of claims 46-49, wherein the first dose of the HER2 antibody is from 5 mg/kg to 10 mg/kg.

51. The use according to claim 50, wherein the first dose of the HER2 antibody is 6 mg/kg or 8 mg/kg.

52. The use according to any one of claims 46-51, wherein the second dose of the HER2 antibody is from 5 to 10 mg/kg.

53. The use according to claim 52, wherein the second dose of the HER2 antibody is 6 mg/kg.

54. The use according to any one of claims 46-53, wherein the first and/or second dose of the HER2 antibody is to be administered by infusion over a period of at least 30 minutes.

55. The use according to any one of claims 46-54, wherein the second dose of the HER2 antibody is to be administered on the same day as the C2D1.

56. The use according to any one of claims 46-55, wherein the C1D2 is at least two-fold the dose of the C1D1.

57. The use according to claim 56, wherein the C1D2 is at least three-fold the dose of the C1D1.

58. The use according to any one of claims 46-57, wherein the C1D1 is from 0.003 mg to 50 mg.

59. The use according to any one of claims 46-58, wherein the C1D2 is from 0.009 mg to 200 mg.

60. The use according to any one of claims 46-59, wherein the C2D1 and the C1D2 are equivalent.
61. The use according to any one of claims 46-59, wherein the C1 further comprises a third dose of the HER2 TDB (C1D3), wherein the C1D3 is greater than the C1D2.
62. The use according to claim 61, wherein the C1D1, the C1D2, and the C1D3 are cumulatively greater than a highest cleared dose of the HER2 TDB in a first dosing cycle of a one-step fractionation, dose-escalation dosing regimen.
63. The use according to claim 62, wherein the highest cleared dose is between about 0.01 mg and about 30 mg.
64. The use according to any one of claims 61-63, wherein the C1D2 is from two-fold to ten-fold the dose of the C1D1.
65. The use according to any one of claims 61-64, wherein the C1D3 is from two-fold to three-fold the dose of the C1D2.
66. The use according to any one of claims 61-65, wherein the C2D1 and the C1D3 are equivalent.
67. The use according to any one of claims 61-66, wherein the C1D1 is from 0.01 mg to 20 mg.
68. The use according to any one of claims 61-67, wherein the C1D2 is from 0.1 mg to 100 mg.
69. The use according to any one of claims 61-68, wherein the C1D3 is from 1 mg to 200 mg.
70. The use according to any one of claims 61-69, wherein the subject is to be administered the C1D1, the C1D2, and the C1D3 on or about Days 1, 8, and 15, respectively, of the C1.
71. The use according to any one of claims 46-70, wherein the length of the C1 is 21 days.
72. The use according to any one of claims 46-71, wherein the length of the C2 is 21 days.
73. The use according to any one of claims 46-72, wherein the subject is to be administered the C2D1 on Day 1 of the C2.
74. The use according to any one of claims 46-73, wherein the use comprises one or more additional dosing cycles.
75. The use according to claim 74, wherein the use comprises up to 15 additional dosing cycles.

76. The use according to claim 74 or 75, wherein the length of each of the one or more additional dosing cycles is 21 days.

77. The use according to any one of claims 74-76, wherein each of the one or more additional dosing cycles comprises a single dose of the HER2 antibody and a single dose of the HER2 TDB.

78. The use according to any one of claims 74-77, wherein the subject is to be administered the HER2 antibody and the HER2 TDB on Day 1 of each of the one or more additional dosing cycles.

79. The use according to claim 78, wherein the HER2 antibody is to be administered prior to the HER2 TDB on Day 1 of each of the one or more additional dosing cycles.

80. Use of a HER2 TDB in the manufacture of a medicament for treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, wherein the use comprises:

(a) a first cycle (C1) comprising a first dose of the HER2 TDB (C1D1) and a second dose of the HER2 TDB (C1D2), wherein the C1D2 is greater than the C1D1; and

(b) a second cycle (C2) comprising an additional dose of the HER2 TDB (C2D1), wherein the C2D1 is equivalent to the highest dose of the HER2 TDB of the C1.

81. The use according to claim 80, wherein the C1D2 is at least two-fold the dose of the C1D1.

82. The use according to claim 81, wherein the C1D2 is at least three-fold the dose of the C1D1.

83. The use according to any one of claims 80-82, wherein the C1D1 is from 0.003 mg to about 10 mg.

84. The use according to any one of claims 80-83, wherein the C1D2 is from 0.009 to about 20 mg.

85. The use according to any one of claims 80-84, wherein the C2D1 and the C1D2 are equivalent.

86. The use according to any one of claims 80-84, wherein the C1 further comprises a third dose of the HER2 TDB (C1D3) which is greater than the C1D2.

87. The use according to claim 86, wherein the C1D1, the C1D2, and the C1D3 are cumulatively greater than a highest cleared dose of the HER2 TDB in a first dosing cycle of a one-step fractionation, dose-escalation dosing regimen.

88. The use according to claim 87, wherein the highest cleared dose is between about 0.01 mg and about 30 mg.

89. The use according to any one of claims 86-88, wherein the C1D2 is from two-fold to ten-fold the dose of the C1D1.

90. The use according to any one of claims 86-89, wherein the C1D3 is from two-fold to three-fold the dose of the C1D2.

91. The use according to any one of claims 86-90, wherein the C2D1 and the C1D3 are equivalent.

92. The use according to any one of claims 86-91, wherein the C1D1 is from 0.01 mg to 20 mg.

93. The use according to any one of claims 86-92, wherein the C1D2 is from 0.1 mg to 100 mg.

94. The use according to any one of claims 86-93, wherein the C1D3 is from 1 mg to 200 mg.

95. The use according to any one of claims 86-94, wherein the subject is to be administered the C1D1, the C1D2, and the C1D3 on or about Days 1, 8, and 15, respectively, of the C1.

96. The use according to any one of claims 80-95, wherein the length of the C1 is 21 days.

97. The use according to any one of claims 80-96, wherein the length of the C2 is 21 days.

98. The use according to any one of claims 80-97, wherein the subject is to be administered the C2D1 on Day 1 of the C2.

99. The use according to any one of claims 80-98, wherein the use comprises one or more additional dosing cycles.

100. The use according to claim 99, wherein the use comprises up to 15 additional dosing cycles.

101. The use according to claim 99 or 100, wherein the length of each of the one or more additional dosing cycles is 21 days.

102. The use according to any one of claims 99-101, wherein each of the one or more additional dosing cycles comprises a single dose of the HER2 TDB.

103. The use according to any one of claims 99-102, wherein the subject is to be administered the HER2 TDB on Day 1 of each of the one or more additional dosing cycles.

104. The use according to any one of claims 47-103, wherein the use results in an increased therapeutic index of the HER2 TDB as compared to use of a control treatment regimen.

105. The use according to any one of claims 1-104, wherein the HER2 antibody and/or the HER2 TDB are to be administered by intravenous infusion.

106. The use according to any one of claims 1-105, further comprising one or more additional therapeutic agents.

107. The use according to claim 106, wherein the one or more additional therapeutic agents are selected from the group consisting of tocilizumab, a corticosteroid, a PD-1 axis antagonist, and an antibody-drug conjugate.

108. The use according to claim 107, wherein the PD-1 axis binding antagonist is selected from the group consisting of a PD-L1 binding antagonist, a PD-1 binding antagonist, and a PD-L2 binding antagonist.

109. The use according to claim 108, wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist.

110. The use according to claim 109, wherein the PD-L1 binding antagonist is selected from the group consisting of MPDL3280A (atezolizumab), YW243.55.S70, MDX-1105, and MEDI4736.

111. The use according to claim 108, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

112. The use according to claim 111, wherein the PD-1 binding antagonist is selected from the group consisting of MDX-1106 (nivolumab), MK-3475 (pembrolizumab), and AMP-224.

113. The use according to claim 108, wherein the PD-1 axis binding antagonist is a PD-L2 binding antagonist.

114. The use according to claim 113, wherein the PD-L2 binding antagonist is an antibody or an immunoadhesin.

115. The use according to any one of claims 1-114, wherein the subject has been administered trastuzumab in a previous treatment regimen.

116. The use according to any one of claims 1-115, wherein the HER2-positive cancer is a HER2-positive solid tumor.

117. The use according to any one of claims 1-116, wherein the HER2-positive cancer is a locally advanced or metastatic HER2-positive cancer.

118. The use according to any one of claims 1-117, wherein the HER2-positive cancer is a HER2-positive breast cancer or a HER2-positive gastric cancer.

119. The use according to any one of claims 1-117, wherein the HER2-positive cancer is selected from the group consisting of a HER2-positive gastroesophageal junction cancer, a HER2-positive colorectal cancer, a HER2-positive lung cancer, a HER2-positive pancreatic cancer, a HER2-positive colorectal cancer, a HER2-positive bladder cancer, a HER2-positive salivary duct cancer, a HER2-positive ovarian cancer, or a HER2-positive endometrial cancer.

120. The use according to claim 119, wherein the HER2-positive lung cancer is a HER2-positive non-small cell lung carcinoma.

121. The use according to claim 119, wherein the HER2-positive ovarian cancer is a HER2-positive epithelial ovarian cancer.