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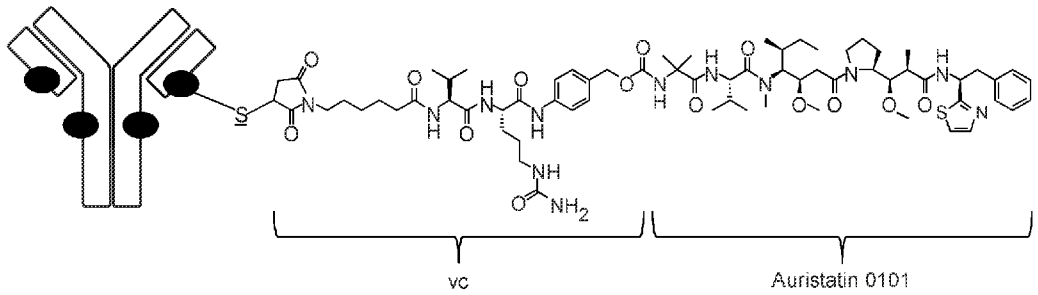
(54) **Title:** TREATMENT WITH SITE SPECIFIC HER2 ANTIBODY-DRUG CONJUGATES

Fig. 1



(57) **Abstract:** The present invention provides for the treatment of patients with pediatric cancer and/or a HER2-expressing pediatric cancer with an anti-HER2 antibody-drug conjugate (ADC). In one embodiment, the anti-HER2 ADC is T(kK183C+K290C)-vc0101 (PF-06804103), in which the antibody T(kK183C+K290C) is linked to the auristatin drug 2-methylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R) -1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(1,3-thiazol-2-yl) ethyl]amino}propyl]pyrrolidin-1-yl }-5-methyl-1-oxoheptan-4-yl]-N- methyl-L-valinamide (also known as "0101") via the cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (also known as "vc").

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TREATMENT WITH SITE SPECIFIC HER2 ANTIBODY-DRUG CONJUGATES

REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 63/060,873 filed on August 4, 2020, the content of which is incorporated herein by reference in its entirety.

REFERENCE TO SEQUENCE LISTING

This application is being filed electronically via EFS-Web and includes an electronically submitted sequence listing in .txt format. The .txt file contains a sequence listing entitled "PC072656ASEQLISTING_ST25.txt" created on June 29, 2021 and having a size of 32 KB. The sequence listing contained in this .txt file is part of the specification and is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to treatment of patients with pediatric cancer and/or Human Epidermal Growth Factor Receptor 2 (HER2)-expressing pediatric cancers. The subject therapeutic regimens involve administration of a site specific HER2 antibody-drug conjugate (ADC) to pediatric patients in need thereof.

BACKGROUND

Members of the ErbB family of transmembrane receptor tyrosine kinases are important mediators of cell growth, cell differentiation, cell migration, and apoptosis. The receptor family includes four distinct members, including epidermal growth factor receptor (EGFR or ErbB1), HER2 (ErbB2 or p185), HER3 (ErbB3) and HER4 (ErbB4 or tyro2).

HER2 was originally identified as the product of the transforming gene from neuroblastomas of chemically treated rats. HER2 overexpression has been validated as tumorigenic both in vitro (Di Fiore et al., 1987, Science 237(4811):178-82; Hudziak et al., 1987, PNAS 84(20):7159-63; Chazin et al., 1992, Oncogene 7(9):1859-66) and in animal models (Guy et al., 1992, PNAS 89(22):10578-82). Amplification of the gene encoding HER2 with consequent overexpression of the receptor occurs in breast and ovarian cancers and correlates with a poor prognosis (Slamon et al., 1987, Science 235(4785):177-82; Slamon et al., 1989, Science 244:707-12; Anbazhagan et al., 1991, Annals Oncology 2(1):47-53; Andrulis et al., 1998, J Clinical Oncology 16(4):1340-9). Overexpression of HER2 (frequently but not necessarily due to gene amplification) has also been observed in other tumor types including gastric, endometrial, non-small cell

lung cancer, colon, pancreatic, bladder, kidney, prostate and cervical (Scholl et al., 2001, Annals Oncology 12 (Suppl. 1):S81-7; Menard et al., 2001, Ann Oncol 12(Suppl 1):S15-9; Martin et al., 2014, Future Oncology 10:1469-86). Herceptin® (trastuzumab) is a humanized monoclonal antibody that binds to the extracellular domain of HER2 (Carter et al. 1992, PNAS 89:4285-9 and US Patent No. 5,821,337). Herceptin® received marketing approval from the Food and Drug Administration on September 25, 1998 for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Although Herceptin® is a breakthrough in treating patients with HER2-overexpressing breast cancers that have received extensive prior anti-cancer therapy, segments of patients in this population fail to respond, respond only poorly or become resistant to Herceptin® treatment.

Kadcyla® (trastuzumab-DM1 or T-DM1) is an antibody drug conjugate consisting of trastuzumab conjugated to the maytansinoid agent DM1 via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate) (Lewis et al., 2008, Cancer Res. 68:9280–90; Krop et al., 2010, J Clin Oncol. 28:2698–2704; US Patent No. 8,337,856). Kadcyla® received marketing approval from the Food and Drug Administration on February 22, 2013 for the treatment of HER2 positive metastatic breast cancer in patients who had been previously treated with Herceptin® and a taxane drug and became Herceptin® refractory. Like seen with Herceptin®, there are segments of the patients in the HER2-overexpressing breast cancer population that do not experience successful long-term therapy with Kadcyla®.

Therefore, there is a significant clinical need for developing further HER2-directed cancer therapies for those patients with HER2-overexpressing tumors or other diseases associated with HER2 overexpression that do not respond, respond poorly or become resistant to current standard of care including, but not limited to, Herceptin® and/or Kadcyla® treatment.

SUMMARY

The present invention provides dosing regimens for the treatment or prophylaxis of pediatric cancer and/or a HER2-expressing pediatric cancer with an anti-HER2 antibody-drug conjugate (ADC). In some aspects of the invention, a dosage regimen comprises administering an effective amount of an anti-HER2 antibody-drug conjugate to a patient at least twice every week, at least weekly (QW), at least every 2 weeks

(Q2W), at least every 3 weeks (Q3W) or at least every 4 weeks (Q4W). In particular aspects of the invention, a dosage regimen comprises administering an effective amount of an anti-HER2 antibody-drug conjugate to a patient every 3 weeks (Q3W).

The present invention also provides methods for the treatment or prophylaxis of pediatric cancer and/or a HER2-expressing pediatric cancer, comprising administering to a patient an effective amount of an anti-HER2 antibody-drug conjugate. In some aspects of the invention, the method comprises administering to the patient an effective amount an anti-HER2 antibody-drug conjugate at least twice every week, at least weekly (QW), at least every 2 weeks (Q2W), at least every 3 weeks (Q3W) or at least every 4 weeks (Q4W). In particular aspects of the invention, the method comprises administering to the patient an effective amount of an anti-HER2 antibody-drug conjugate (ADC) every 3 weeks (Q3W).

The present invention also provides anti-HER2 antibody-drug conjugates for use in the treatment or prophylaxis of pediatric cancer and/or HER2-expressing pediatric cancers. The present invention also provides uses of an anti-HER2 antibody-drug conjugate in the treatment or prophylaxis of pediatric cancer and/or a HER2-expressing pediatric cancer. The present invention also provides uses of an anti-HER2 antibody-drug conjugate in the manufacture of a medicament for treatment or prophylaxis of pediatric cancer and/or a HER2-expressing pediatric cancer. The present invention also provides pharmaceutical compositions comprising an anti-HER2 antibody-drug conjugate for use in the treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer.

In some aspects of the invention, administration of, or use of, a pharmaceutical composition or formulation comprising an anti-HER2 antibody-drug conjugate is contemplated.

The present invention also provides anti-HER2 antibody-drug conjugates formulated as a pharmaceutical composition. The present invention also provides methods of preparing and manufacturing anti-HER2 antibody-drug conjugates and pharmaceutical compositions comprising the same. The present invention also provides article of manufacture and kits comprising the pharmaceutical compositions disclosed herein.

In some aspects of the invention, the anti-HER2 antibody-drug conjugate is administered or is administrable at a dose of about 0.10 mg/kg to about 10 mg/kg or any

range of dosages between these values. In another aspect of the invention, the anti-HER2 antibody-drug conjugate is administered or is administrable at a dose of about 0.10 mg/kg to about 5 mg/kg, about 0.10 mg/kg to about 1 mg/kg, or about 0.10 mg/kg to about 0.50 mg/kg. In some aspects of the invention, the anti-HER2 antibody-drug conjugates is administered or is administrable at a dose of at least 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.95, 1.00, 1.10, 1.20, 1.30, 1.40, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00 mg/kg. In some aspects of the invention, dosages of about 0.15 mg/kg, 0.50 mg/kg, 1.20 mg/kg, 2.00 mg/kg, 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg are particularly contemplated. Preferably, the anti-HER2 antibody-drug conjugate is administered or is administrable at a dose of about 3, 4, or 5 mg/kg. In a particular aspect of the invention, the anti-HER2 antibody-drug conjugate is administered or is administrable at least twice every week, at least weekly (QW), at least every 2 weeks (Q2W), at least every 3 weeks (Q3W) or at least every 4 weeks (Q4W). Preferably, the anti-HER2 antibody-drug conjugate is administered or is administrable every 3 weeks (Q3W). In a particular aspect of the invention, the anti-HER2 antibody-drug conjugate is administered or is administrable every 3 weeks (Q3W) at a dose of about 0.15 mg/kg, 0.50 mg/kg, 1.20 mg/kg, 2.00 mg/kg, 2.70 mg/kg, 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg.

In some aspects of the invention, the anti-HER2 antibody-drug conjugates of the present invention comprise an antibody comprising three CDRs from a heavy chain variable region (VH) having the amino acid sequence shown in SEQ ID NO: 1 and three CDRs from a light chain variable region (VL) having the amino acid sequence shown in SEQ ID NO: 7. In another aspect of the invention, anti-HER2 antibody-drug conjugates comprise an antibody comprising a VH CDR1 having the amino acid sequence shown in SEQ ID NO: 2, VH CDR2 having the amino acid sequence shown in SEQ ID NO: 3, and VH CDR3 having the amino acid sequence shown in SEQ ID NO: 4, and/or VL CDR1 having the amino acid sequence shown in SEQ ID NO: 8, VL CDR2 having the amino acid sequence shown in SEQ ID NO: 9, and VL CDR3 having the amino acid sequence shown in SEQ ID NO: 10. In some aspects of the invention, the anti-HER2 antibody-drug conjugates comprise an antibody comprising a heavy chain protein having the amino acid sequence shown in SEQ ID NO: 14 and a light chain protein having the amino acid sequence shown in SEQ ID NO: 16. In a particular aspect of the invention, the anti-HER2 antibody-drug conjugate comprises an antibody designated T(kK183C+K290C), which is

described in U.S. Patent Publication No. 2017/0151341 and International Patent Application Publication WO 2017/093844, each of which is herein incorporated by reference in its entirety. In another aspect of the invention, the anti-HER2 antibody-drug conjugate further comprises a drug and a linker, wherein the drug is the auristatin drug 2-methylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (also known as "0101")) (Table 2 *infra*),and the linker is the cleavable linker maleimidocaproyl–valine-citrulline-p-aminobenzyloxycarbonyl (also known as "vc") (Table 2 *infra*). In a particular aspect, the anti-HER2 antibody-drug conjugate is T(kK183C+K290C)-vc0101 ADC (see Fig. 1).

In some aspects of the invention, the HER2-expressing pediatric cancer to be treated with the site specific HER2 ADCs of the invention can express HER2 at a high, moderate or low level. In some embodiments, the pediatric cancer to be treated is resistant to, refractory to and/or relapsed from treatment with trastuzumab and/or trastuzumab emtansine (T-DM1) either of which alone or in combination with a taxane. Pediatric cancers to be treated include, but are not limited to, ependymoma, astrocytoma, glioblastoma, high grade glioma, medulloblastoma, B-cell acute lymphoblastic leukemia (B-cell ALL), atypical teratoid/rhabdoid tumor (AT/RT), neuroblastoma, osteosarcoma or sarcoma.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides the structure of the anti-HER2 immunoglobulin G1 ADC, T(kK183C+K290C)-vc0101, which comprises the anti-HER2 antibody T(kK183C+K290C), 0101 payload with vc linker. Each black circle represents a linker/payload that is conjugated to the monoclonal antibody. The underlined entity is supplied by the amino acid residue on the antibody through which conjugation occurs.

DETAILED DESCRIPTION

HER2 is a receptor tyrosine kinase that is involved in the regulation of various cellular functions. Aberrant HER2 receptor activation has been implicated as a driving factor in the tumorigenesis and progression of a number of cancers, including pediatric cancers.

ADCs are a class of drugs that use antibodies specifically targeting tumor-associated antigens as vehicles to deliver covalently attached small-molecule toxins into

cancer cells. T-DM1 is built upon this principle and it consists of trastuzumab coupled with the microtubule poison maytansinoid emtansine (DM1) through a thioether linker. Approval of T-DM1 by the U.S. Food and Drug Administration in February 2013 is mainly based on the key data derived from a phase III clinical trial investigating the efficacy and safety of T-DM1 in HER2-positive metastatic breast cancer patients. T-DM1 treatment prolonged overall survival by 5–6 months with an objective response rate of 44%. While these results are encouraging, they also reveal the limitation of T-DM1 in efficacy. Receptor tyrosine kinases are typically routed to lysosomes for degradation following ligand binding, which is a major, negative feedback mechanism regulating the intensity and duration of receptor activation. Unlike most receptor tyrosine kinases, HER2 has no natural ligand and it appears to be impaired in lysosomal trafficking. Instead, HER2 is largely recycled back to the plasma membrane following spontaneous endocytosis. Correspondingly, the majority of internalized T-DM1 passively recycles with HER2 back to the cell surface and only a small fraction of T-DM1 is routed to lysosomes for degradation. Since the amount of toxin released into the cytoplasm determines the cell killing potency of an ADC, this may explain the lack of activity with T-DM1 in tumors expressing low levels of HER2. In this regard, it is likely that an improvement in ADC-mediated internalization and lysosomal trafficking would significantly enhance the cytoplasmic delivery of toxins, which may result in the killing of cancer cell populations that express a broader range of HER2.

The present invention provides the treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer with an anti-HER2 antibody-drug conjugate (ADC) or a pharmaceutical composition comprising the same. In some aspects of the invention, a dosage regimen may comprise administering an effective amount of an anti-HER2 antibody-drug conjugate to a patient at least twice every week, at least weekly (QW), at least every 2 weeks (Q2W), at least every 3 weeks (Q3W) or at least every 4 weeks (Q4W). In particular aspects of the invention, a dosage regimen may comprise administering an effective amount of an anti-HER2 antibody-drug conjugate to a patient every 3 weeks (Q3W). In particular aspects of the invention, the efficacy of the dosage regimen may be determined by measuring the decrease in tumor size as compared to the tumor size in the patient prior to the initial administration of the anti-HER2 antibody-drug conjugate. For example, the tumor may decrease in size by at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least

40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or up to 100%, or up to a point at which the tumor is no longer detectable. The present invention also provides methods for the treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer comprising administering an anti-HER2 ADC or pharmaceutical composition comprising the same to a patient. The present invention further provides methods for the treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer in which an anti-HER2 ADC or pharmaceutical composition comprising the same is intravenously administered to a patient every 3 weeks (Q3W).

The present invention also provides anti-HER2 ADCs and pharmaceutical compositions comprising the same for use in the treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer. The present invention further provides anti-HER2 ADCs or pharmaceutical compositions comprising the same for use in the treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer in which the anti-HER2 ADC or pharmaceutical composition comprising the same is intravenously administrable or administered to a patient every 3 weeks (Q3W).

The present invention also provides uses of an anti-HER2 ADC or pharmaceutical composition comprising the same for treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer. The present invention further provides uses of an anti-HER2 ADC or pharmaceutical composition comprising the same for treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer in which an anti-HER2 ADC or pharmaceutical composition comprising the same is intravenously administrable or administered to a patient every 3 weeks (Q3W).

The present invention also provides uses of an anti-HER2 ADC in the manufacture of a medicament for treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer.

The present invention also provides pharmaceutical compositions comprising an anti-HER2 ADC for use in the treatment or prophylaxis of a pediatric cancer and/or a HER2-expressing pediatric cancer.

The present invention also provides anti-HER2 ADCs and pharmaceutical compositions comprising the same for use in the treatment or prophylaxis of a condition associated with HER2 expression in a patient. The conditions associated with HER2

expression include, but are not limited to, abnormal HER2 expression, altered or aberrant HER2 expression, HER2 overexpression, and a proliferative disorder (e.g., cancer).

The present invention also provides methods for the treatment or prophylaxis of a condition associated with HER2 expression in a patient comprising administering an anti-HER2 ADC or pharmaceutical composition comprising the same to the patient.

The present invention also provides uses of an anti-HER2 ADC or pharmaceutical composition comprising the same for treatment or prophylaxis of a condition associated with HER2 expression in a patient.

The present invention also provides uses of an anti-HER2 ADC in the manufacture of a medicament for treatment or prophylaxis of a condition associated with HER2 expression in a patient.

The present invention also provides pharmaceutical compositions for use in the treatment or prophylaxis of a condition associated with HER2 expression in a patient.

The present invention also provides anti-HER2 ADCs and pharmaceutical compositions comprising the same for use in inhibiting growth or progression of a HER2-expressing tumor in a patient.

The present invention also provides methods for inhibiting growth or progression of a HER2-expressing tumor in a patient comprising administering an anti-HER2 ADC or pharmaceutical composition comprising the same to the patient.

The present invention also provides uses of an anti-HER2 ADC or pharmaceutical composition comprising the same for inhibiting growth or progression of a HER2-expressing tumor in a patient.

The present invention also provides uses of an anti-HER2 ADC in the manufacture of a medicament for inhibiting growth or progression of a HER2-expressing tumor.

The present invention also provides pharmaceutical compositions comprising an anti-HER2 ADC for use in inhibiting growth or progression of an HER2-expressing tumor.

The present invention also provides anti-HER2 ADCs and pharmaceutical compositions comprising the same for use in inhibiting metastasis of HER2-expressing cancer cells in a patient.

The present invention also provides methods for inhibiting metastasis of HER2-expressing cancer cells in a patient comprising administering an anti-HER2 ADC or pharmaceutical composition comprising the same to the patient.

The present invention also provides uses of an anti-HER2 ADC or pharmaceutical composition comprising the same for inhibiting metastasis of HER2-expressing pediatric cancer cells in a patient.

The present invention also provides uses of an anti-HER2 ADC in the manufacture of a medicament for inhibiting metastasis of HER2-expressing pediatric cancer cells.

The present invention also provides pharmaceutical compositions comprising an anti-HER2 ADC for use in inhibiting metastasis of HER2-expressing pediatric cancer cells.

The present invention also provides anti-HER2 ADCs and pharmaceutical compositions comprising the same for use in inducing regression of a HER2-expressing tumor in a patient.

The present invention also provides methods for inducing regression of a HER2-expressing tumor in a patient comprising administering an anti-HER2 ADC or pharmaceutical composition comprising the same to the patient.

The present invention also provides uses of an anti-HER2 ADC or pharmaceutical composition comprising the same for inducing regression of a HER2-expressing tumor in a patient.

The present invention also provides uses of an anti-HER2 ADC in the manufacture of a medicament for inducing regression of a HER2-expressing tumor.

The present invention also provides pharmaceutical compositions comprising an anti-HER2 ADC for use in inducing regression of a HER2-expressing tumor.

The present invention also provides anti-HER2 antibody-drug conjugates formulated as a pharmaceutical composition. The present invention also provides methods of preparing and manufacturing anti-HER2 antibody-drug conjugates and pharmaceutical compositions comprising the same. The present invention also provides articles of manufacture and kits comprising the pharmaceutical compositions disclosed herein.

General Techniques

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, Molecular Cloning: A Laboratory Manual, second edition (Sambrook et al., 1989) Cold Spring Harbor Press;

Oligonucleotide Synthesis (M.J. Gait, ed., 1984); Methods in Molecular Biology, Humana Press; Cell Biology: A Laboratory Notebook (J.E. Gellis, ed., 1998) Academic Press; Animal Cell Culture (RI. Freshney, ed., 1987); Introduction to Cell and Tissue Culture (J.P. Mather and P.E. Roberts, 1998) Plenum Press; Cell and Tissue Culture: Laboratory Procedures (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., 1993-1998) J. Wiley and Sons; Methods in Enzymology (Academic Press, Inc.); Handbook of Experimental Immunology (D.M. Weir and C.C. Blackwell, eds.); Gene Transfer Vectors for Mammalian Cells (J.M. Miller and M.P. Calos, eds., 1987); Current Protocols in Molecular Biology (F.M. Ausubel et al., eds., 1987); PCR: The Polymerase Chain Reaction, (Mullis et al., eds., 1994); Current Protocols in Immunology (J.E. Coligan et al., eds., 1991); Short Protocols in Molecular Biology (Wiley and Sons, 1999); Immunobiology (C.A. Janeway and P. Travers, 1997); Antibodies (P. Finch, 1997); Antibodies: a practical approach (D. Catty., ed., IRL Press, 1988-1989); Monoclonal antibodies: a practical approach (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); Using antibodies: a laboratory manual (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); The Antibodies (M. Zanetti and J.D. Capra, eds. Harwood Academic Publishers, 1995).

As used herein, the terms “antibody-drug conjugate” or ”ADC” are used interchangeably and refer to antibodies, or antigen-binding fragments thereof, including antibody derivatives that bind to HER2 and are conjugated to a drug such as a cytotoxic, cytostatic, and/or therapeutic agent, as described herein. For example, a cytotoxic agent can be linked or conjugated to an anti-HER2 antibody as described herein for targeted local delivery of the cytotoxic agent to tumors (e.g., HER2 expressing tumors). Thus, the antibody-drug conjugates of the present invention comprise an antibody, or antigen-binding fragment thereof, that binds to HER2, and a linker-drug moiety.

As used herein, the term “HER2” refers to a transmembrane tyrosine kinase receptor that belongs to the EGFR family. HER2 is also known as ErbB2, p185 and CD340. This family of receptors includes four members (EGFR/HER1, HER2, HER3 and HER4) that function by stimulating growth factor signaling pathways such as the PI3K–AKT–mTOR pathway. Amplification and/or overexpression of HER2 is associated with multiple human malignancies. The wild type human HER2 protein is described, for example, in Semba et al., 1985, PNAS 82:6497-6501 and Yamamoto et al., 1986, Nature 319:230-4 and Genbank Accession Number X03363. The term “HER2” includes variants, isoforms, homologs, orthologs and paralogs. In some aspects of the invention,

antibodies and antibody-drug conjugates cross-react with HER2 from species other than human, such as HER2 of mouse, rat, or primate, as well as different forms of HER2 (e.g., glycosylated HER2). In other aspects, the antibodies and antibody-drug conjugates may be completely specific for human HER2 and may not exhibit species or other types of cross-reactivity. As used herein the term HER2 refers to naturally occurring human HER2 unless contextually dictated otherwise. Therefore, a "HER2 antibody", “anti-HER2 antibody”, or other similar designation, means any antibody (as defined herein) that associates, binds or reacts with the HER2 type ligand or isoform, or fragment or derivative thereof. Further, a "HER2 antibody-drug conjugate", “anti-HER2 antibody-drug conjugate” means any antibody-drug conjugate or ADC (as defined herein) that associates, binds or reacts with the HER2 type ligand or isoform, or fragment or derivative thereof. HER2 is overexpressed in tumor versus normal tissue in a number of human tumors.

The antibody used in the present invention specifically binds to HER2. In a specific embodiment, the HER2 antibody binds to the same epitope on HER2 as trastuzumab (Herceptin®). In a more specific embodiment, the HER2 antibody has the same variable region CDRs as trastuzumab (Herceptin®). In yet a more specific embodiment, the HER2 antibody has the same variable regions (i.e., V_H and V_L) as trastuzumab (Herceptin®).

As used herein, the term “linker” describes the direct or indirect linkage of the antibody to the drug payload. Attachment of a linker to an antibody can be accomplished in a variety of ways, such as through surface lysines, reductive-coupling to oxidized carbohydrates, cysteine residues liberated by reducing interchain disulfide linkages, reactive cysteine residues engineered at specific sites, and acyl donor glutamine-containing tag or an endogenous glutamine made reactive by polypeptide engineering in the presence of transglutaminase and an amine. The present invention uses site specific methods to link the antibody to the drug payload. In one embodiment, conjugation occurs through cysteine residues that have been engineered into the antibody constant region. In another embodiment, conjugation occurs through acyl donor glutamine residues that have either been a) added to the antibody constant region via a peptide tag, b) engineered into the antibody constant region or c) made accessible/reactive by engineering surrounding residues. Linkers can be cleavable (i.e., susceptible to cleavage under intracellular conditions) or non-cleavable. In some embodiments, the linker is a cleavable linker. In a particular aspect of the invention, the linker of the HER2 antibody

drug conjugate of the invention includes, but is not limited to, maleimidocaproyl–valine-citrulline-p-aminobenzyloxycarbonyl (hereinafter “vc”).

As used herein, the term “drug”, “payload” or “compound” refer to any therapeutic agent useful in treating cancer. The drug has biological or detectable activity, for example, cytotoxic agents, chemotherapeutic agents, cytostatic agents, and immunomodulatory agents. In preferred embodiments, therapeutic agents have a cytotoxic effect on tumors including the depletion, elimination and/or the killing of tumor cells. The terms drug, payload, and drug payload are used interchangeably. In a specific embodiment, the drug is an anti-mitotic agent. In a more specific embodiment, the drug is an auristatin. In a yet more specific embodiment, the drug is 2-methylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (also known as 0101). In some embodiments, the drug is preferably membrane permeable.

As used herein, the term “linker-drug moiety” refers to the molecule resulting from a drug linked or conjugated to a linker.

As used herein, the terms "binding affinity" or “K_D” refers to the equilibrium dissociation constant of a particular antigen-antibody interaction. The K_D is the ratio of the rate of dissociation, also called the "off-rate” or “k_d", to the rate of association, or "on-rate” or “k_a". Thus, K_D equals k_d/ k_a and is expressed as a molar concentration (M). It follows that the smaller the K_D, the stronger the binding affinity. Therefore, a K_D of 1 μM indicates weak binding affinity compared to a K_D of 1 nM. K_D values for antibodies can be determined using methods well established in the art. One method for determining the K_D of an antibody is by using surface plasmon resonance, typically using a biosensor system such as a BIACORE® system.

An “antibody” or “Ab” is an immunoglobulin molecule capable of recognizing and binding to a specific target or antigen, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term “antibody” can encompass any type of antibody, including but not limited to monoclonal antibodies, polyclonal antibodies, “antigen-binding fragments” (or portion), such as Fab, Fab’, $F(ab')_2$, Fd, Fv, Fc, etc., of intact antibodies that retain the ability to specifically bind to a given antigen (e.g. HER2), an isolated complementarity determining region (CDR), bispecific

antibodies, heteroconjugate antibodies, mutants thereof, fusion proteins having an antibody, or antigen-binding fragment thereof, (e.g., a domain antibody), single chain (ScFv) and single domain antibodies (*e.g.*, shark and camelid antibodies), maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, e.g., Holliger and Hudson, 2005, Nature Biotechnology 23(9): 1126-1136), humanized antibodies, chimeric antibodies and any other modified configuration of the immunoglobulin molecule that includes an antigen recognition site of the required specificity, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies. The antibodies may be of murine, rat, human, or any other origin (including chimeric or humanized antibodies). In some aspects of the invention, the antibody, or antigen-binding fragment thereof, of the disclosed anti-HER2 antibody-drug conjugates is a chimeric, humanized, or a recombinant human antibody, or HER2-binding fragment thereof.

A "variable region" of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. As known in the art, the variable regions of the heavy and light chain each consist of four framework regions (FR) connected by three complementarity determining regions (CDRs) also known as hypervariable regions. The CDRs in each chain are held together in close proximity by the FRs and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al. Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda MD)); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Al-Lazikani et al., J. Molec. Biol. 273:927-948 (1997)). As used herein, a CDR may refer to CDRs defined by either approach or by a combination of both approaches.

A CDR of a variable domain are comprised of amino acid residues within the variable region that are identified in accordance with the definitions of Kabat, Chothia, the accumulation of both Kabat and Chothia, VBASE2, AbM, contact, and/or conformational definitions or any method of CDR determination well known in the art. Antibody CDRs may be identified as the hypervariable regions originally defined by Kabat et al. See, e.g., Kabat et al., 1992, Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, NIH, Washington D.C. The positions of the CDRs may also

be identified as the structural loop structures originally described by Chothia and others. See, e.g., Chothia et al., Nature 342:877-883, (1989). The CDR positions may also be derived from an analysis of the VBASE2 database. (See, e.g. Retter et al., Nucleic Acids Res. 33(Database Issue): D671-D674, 2005).

Other approaches to CDR identification include the "AbM definition," which is a compromise between Kabat and Chothia and is derived using Oxford Molecular's AbM antibody modeling software (now ACCELRYS®), or the "contact definition" of CDRs based on observed antigen contacts, set forth in MacCallum et al., J. Mol. Biol., 262:732-745, (1996). In another approach, referred to herein as the "conformational definition" of CDRs, the positions of the CDRs may be identified as the residues that make enthalpic contributions to antigen binding. See, e.g., Makabe et al., Journal of Biological Chemistry, 283:1156-1166, 2008. Still other CDR boundary definitions may not strictly follow one of the above approaches, but will nonetheless overlap with at least a portion of the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. As used herein, a CDR may refer to CDRs defined by any approach known in the art, including combinations of approaches. The methods used herein may utilize CDRs defined according to any of these approaches. For anti-HER2 antibody-drug conjugates described herein, CDRs may be defined in accordance with any of Kabat, Chothia, extended, VBASE2, AbM, contact, and/or conformational definitions.

In other aspects of the invention, the anti-HER2 antibody-drug conjugates comprise an antibody or antigen-binding fragment thereof that further comprises one or more CDR(s) of the antibody or antigen-binding fragment thereof (such as one, two, three, four, five, or all six CDRs).

Antibodies, antibody domains, and antigen-binding fragments thereof may be described as "polypeptides", "oligopeptides", "peptides" and "proteins", i.e., chains of amino acids of any length, preferably, relatively short (e.g., 10-100 amino acids). The chain may be linear or branched, it may comprise modified amino acids, and/or may be interrupted by non-amino acids. The terms also encompass an amino acid chain that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the

definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that the polypeptides can occur as single chains or associated chains. Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Commission on Biochemical Nomenclature.

As used herein, "humanized antibody" or “CDR grafted antibody” refers to forms of non-human (e.g. murine) antibodies that are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen binding subsequences of antibodies) that contain minimal sequences derived from a non-human immunoglobulin. Preferably, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from one or more complementarity determining regions (CDRs) of the recipient are replaced by residues from one or more CDRs of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity.

As used herein, the term "dosing regimen" refers to the total course of treatment administered to a patient, e.g., treatment with an anti-HER2 ADC.

As used herein, “dose limiting toxicity” (DLT) refers to the dosage of the anti-HER2 antibody-drug conjugate that is contraindicative of a further increase in dosage. DLT is graded according to NCI Common Terminology Criteria (v 4.03) during the first cycle of treatment which is not clearly and incontrovertibly due to underlying disease/progression or extraneous cause. Hematologic: grade 4 neutropenia for >7 days; febrile neutropenia; grade ≥3 neutropenia with infection; thrombocytopenia with clinically significant bleeding; or grade 4 thrombocytopenia. Non-hematologic: grade ≥3 toxicities, that are considered clinically significant, excluding nausea, vomiting or diarrhea or electrolyte abnormality lasting <72 hours, that does not resolve spontaneously or does not respond to conventional medical interventions or other supportive care; or delay by more than 2 weeks in receiving the next scheduled cycle due to persisting toxicities.

As used herein “maximum tolerated dose” (MTD) refers to the highest dosage of the anti-HER2 antibody-drug conjugate that does not cause unacceptable side effects or intolerable toxicities. MTD is estimated using the mTPI based on observed DLT rate, with a target DLT rate of 27.5% and equivalence interval of 22.5-32.5%. At least 9 patients will be accumulated at a dose that is predicted to be the MTD.

The disclosed anti-HER2 antibody-drug conjugates may be administered as an initial treatment, or for treatment of conditions that are unresponsive to conventional therapies. In addition, the HER2 antibody-drug conjugates may be used in combination with other therapies (e.g., surgical excision, radiation, additional anti-cancer drugs, etc.) to thereby elicit additive or potentiated therapeutic effects and/or reduce toxicity of some anti-cancer agents. HER2 antibody-drug conjugates of the invention may be co-administered or co-formulated with additional agents or formulated for consecutive administration with additional agents in any order.

As used herein, the phrases “effective amount” or “effective dosage” are used interchangeably and refer to an amount of a drug (e.g., anti-HER2 antibody-drug conjugate), compound, or pharmaceutical composition necessary to achieve one or more beneficial or desired prophylactic or therapeutic results. For prophylactic use, beneficial or desired results include eliminating or reducing the risk of developing a disease (e.g., cancer and/or HER2-expressing cancer), delaying the onset of the disease, or preventing the progression of the disease. For therapeutic use, beneficial or desired results include eliminating, reducing the incidence of, or ameliorating one or more symptoms of, these diseases or conditions. Determination of an effective amount or dosage may include observing or measuring changes in biochemical or histological markers; behavioral symptoms of the disease; complications of the disease; and intermediate pathological phenotypes presenting during development of the disease. Determination of an effective amount or dosage may also include observing or measuring a decrease in the dose of another drug/medication required to treat the disease; or an increase in the efficacy of another drug/medication. In particular aspects of the invention, the efficacy of treatment may be determined by measuring the decrease in tumor size as compared to the tumor size in the patient prior to the initial administration of the anti-HER2 antibody-drug conjugate using methods known in the art (e.g., Response Evaluation Criteria In Solid Tumors (RECIST)). For example, the tumor may decrease in size by at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or up to 100% or up to a point at which the tumor is no longer detectable.In one aspect, the invention provides a method for treating a condition associated with HER2 expression in a patient. The invention also provides an antibody-drug conjugate, or a pharmaceutical

composition, as described herein, for use in a method for treating a condition associated with HER2 expression in a patient. The invention further provides the use of an antibody-drug conjugate, or a pharmaceutical composition, as described herein, in the manufacture of a medicament for treating a condition associated with HER2 expression in a patient.

In some aspects of the invention, the method of treating a condition associated with HER2 expression in a patient includes administering to the patient in need thereof an effective amount of a composition (e.g., pharmaceutical composition) comprising a HER2 antibody-drug conjugate as described herein. The conditions associated with HER2 expression include, but are not limited to, abnormal HER2 expression, altered or aberrant HER2 expression, HER2 overexpression, and a proliferative disorder (e.g., cancer).

In some aspects of the invention, the HER2-expressing pediatric cancer to be treated with the site specific HER2 ADCs of the invention can express HER2 at a high, moderate or low level. In some embodiments, the pediatric cancer to be treated is resistant to, refractory to and/or relapsed from treatment with trastuzumab and/or trastuzumab emtansine (T-DM1) either of which alone or in combination with a taxane. Pediatric cancers to be treated include, but are not limited to, ependymoma, astrocytoma, glioblastoma, high grade glioma, medulloblastoma, B-cell acute lymphoblastic leukemia (B-cell ALL), atypical teratoid/rhabdoid tumor (AT/RT), neuroblastoma, osteosarcoma or sarcoma. In a more specific embodiment, the pediatric cancer is ependymoma. In another embodiment, the pediatric cancer is atypical teratoid/rhabdoid tumor (AT/RT). In another embodiment, the pediatric cancer is neuroblastoma.

In some aspects of the invention, provided is a method of inhibiting tumor growth or progression in a patient who has a HER2 expressing tumor, including administering to the patient in need thereof an effective amount of a composition having the HER2 antibody-drug conjugates as described herein. In other aspects of the invention, provided is a method of inhibiting metastasis of HER2 expressing pediatric cancer cells in a patient, including administering to the patient in need thereof an effective amount of a composition having the HER2 antibody-drug conjugates as described herein. In other aspects of the invention, provided is a method of inducing regression of a HER2 expressing tumor regression in a patient, including administering to the patient in need thereof an effective amount of a composition having the HER2 antibody-drug conjugates as described herein.

In other aspects, the invention provides an antibody-drug conjugate, or a pharmaceutical composition, as described herein, for use in a method as described above. In other aspects, the invention provides the use of an antibody-drug conjugate, or a pharmaceutical composition, as described herein, in the manufacture of a medicament for use in the methods described above.

As used herein, the terms "individual", "subject", and “patient” are used interchangeably and refer to a mammal, including, but not limited to, farm animals, sport animals, pets, primates, horses, dogs, cats, mice and rats. In a preferred aspect of the invention, the mammal is a human.

As used herein, the term “pediatric” or “pediatric cancer” refer to a patient or cancer in a patient who is under the age of 21 years at the time of diagnosis or treatment. The term “pediatric” can be further divided into various subpopulations including: neonates (from birth through the first 28 days of life); infants (29 days of age to less than two years of age); children (two years of age to less than 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). See, e.g., Berhman RE, Kliegman R, Arvin AM, Nelson WE. Nelson *Textbook of Pediatrics,* 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, et al. *Rudolph's Pediatrics*, 21st Ed. New York: McGraw-Hill, 2002; and Avery MD, First LR. *Pediatric Medicine*, 2nd Ed. Baltimore: Williams & Wilkins; 1994.

In some embodiments, the patient is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, the patient is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 1 years of age, from 10 years of age to less than 15 years of age, or from 1 years of age to less than 22 years of age.

As used herein, the terms "pharmaceutically acceptable carrier" and "pharmaceutical acceptable excipient" are used interchangeably and refer to any material

which, when combined with an active ingredient, allows the ingredient to retain biological activity and is non-reactive with the patient's immune system. Examples include, but are not limited to, any of the standard pharmaceutical carriers such as a phosphate buffered saline solution, water, emulsions such as oil/water emulsion, and various types of wetting agents. Compositions comprising such carriers are formulated by well-known conventional methods (see, for example, Remington's Pharmaceutical Sciences, 18th edition, A. Gennaro, ed., Mack Publishing Co., Easton, PA, 1990; and Remington, The Science and Practice of Pharmacy, 20th Ed., Mack Publishing, 2000).

Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. For example, description referring to "about X" includes description of "X." Numeric ranges are inclusive of the numbers defining the range.

It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of' and/or "consisting essentially of' are also provided.

Additional scientific and technical terms used in connection with the present invention, unless indicated otherwise herein, shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclature used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics, and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used in the art.

Dosing Regimens

The present invention provides for dosing levels, dosing regimens and methods for the treatment of patients with cancer and/or an HER2-expressing cancer with an anti-HER2 antibody-drug conjugate (ADC). The present invention further provides for dosing levels, dosing regimens and methods for the treatment of patients with cancer and/or a HER2-expressing cancer in which an anti-HER2 ADC is administered to a patient intravenously, subcutaneously, intramuscularly, by bolus injection, intracerebrally, intracranially or by sustained release. Preferably, the anti-HER2 ADC is administered to a patient intravenously. The present invention further provides for dosing levels, dosing regimens and methods for the treatment of patients with cancer and/or a HER2-

expressing cancer in which an anti-HER2 ADC administered to a patient at least twice every week, at least weekly (QW), at least every 2 weeks (Q2W), at least every 3 weeks (Q3W) or at least every 4 weeks (Q4W). Preferably, an anti-HER2 ADC is administered to a patient every 3 weeks (Q3W). The present invention further provides for dosing levels, dosing regimens and methods for the treatment of patients with cancer and/or a HER2-expressing cancer in which an anti-HER2 ADC is administered to a patient intravenously every 3 weeks (Q3W).

In some aspects of the invention, the anti-HER2 antibody-drug conjugate is administered or is administrable at a dose of about 0.10 mg/kg to about 10 mg/kg or any range of dosages between these values. In another aspect of the invention, the anti-HER2 antibody-drug conjugate is administered or is administrable at a dose of about 0.10 mg/kg to about 5 mg/kg, about 0.10 mg/kg to about 1 mg/kg, or about 0.10 mg/kg to about 0.50 mg/kg. In some aspects of the invention, the anti-HER2 antibody-drug conjugates is administered or is administrable at a dose of at least 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.95, 1.00, 1.10, 1.20, 1.30, 1.40, 1.50, 2.00, 2.50, 2.70, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00 mg/kg. Preferably, the anti-HER2 antibody-drug conjugate is administered or is administrable at a dose of about 0.5 mg/kg to 6 mg/kg. Preferably, the anti-HER2 antibody-drug conjugate is administered or is administrable at a dose of about 3 mg/kg to 6 mg/kg. Preferably, the anti-HER2 antibody-drug conjugate is administered or is administrable at a dose of about 3, 4, or 5 mg/kg. In some aspects of the invention, dosages of about 0.15 mg/kg, 0.50 mg/kg, 1.20 mg/kg, 2.00 mg/kg, 2.70 mg/kg, 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg are particularly contemplated. In a particular aspect of the inventionthe anti-HER2 antibody-drug conjugate is administered or is administrable every 3 weeks (Q3W) at a dose of about 0.15 mg/kg, 0.50 mg/kg, 1.20 mg/kg, 2.00 mg/kg, 2.70 mg/kg, 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg. In a particular aspect of the invention the anti-HER2 antibody-drug conjugate is administered or is administrable every 3 weeks (Q3W) at a dose of about 3 mg/kg or 4mg/kg.

The present invention further provides for dosing levels, dosing regimens and methods for the treatment of patients with cancer and/or a HER2-expressing cancer in which the treatment results in a decrease in a tumor size of at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%,

at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or 100% as compared to the tumor size in the patient prior to initial administration of the anti-HER2 antibody-drug conjugate. A decrease in tumor size may be measured or determined by any method used and accepted in the art (e.g., RECIST v.1.1).

Anti-HER2 Antibody-Drug Conjugates (ADCs)

The invention can be practiced using, for example, an anti-HER2 ADC comprising an antibody that specifically binds to human HER2. In some aspects of the invention, the invention can be practiced using the anti-HER2 antibody-drug conjugates of the present invention that comprises an antibody comprising three CDRs from a heavy chain protein having the amino acid sequence shown in SEQ ID NO: 14 and three CDRs from a light chain protein having the amino acid sequence shown in SEQ ID NO: 16. In another aspect of the invention, anti-HER2 antibody-drug conjugates comprise an antibody comprising a VH CDR1 having the amino acid sequence shown in SEQ ID NO: 2, VH CDR2 having the amino acid sequence shown in SEQ ID NO: 3, and VH CDR3 having the amino acid sequence shown in SEQ ID NO: 4, and/or VL CDR1 having the amino acid sequence shown in SEQ ID NO: 8, VL CDR2 having the amino acid sequence shown in SEQ ID NO: 9, and VL CDR3 having the amino acid sequence shown in SEQ ID NO: 10. In another aspect of the invention, the anti-HER2 antibody-drug conjugates comprise an antibody comprising a VH CDR1 having the amino acid sequence shown in SEQ ID NO: 2, VH CDR2 having the amino acid sequence shown in SEQ ID NO: 3, a VH CDR3 having the amino acid sequence shown in SEQ ID NO: 4, a VL CDR1 having the amino acid sequence shown in SEQ ID NO: 8, VL CDR2 having the amino acid sequence shown in SEQ ID NO: 9, a VL CDR3 having the amino acid sequence shown in SEQ ID NO: 10, a heavy chain constant region having the amino acid sequence shown in SEQ ID NO: 13 and a light chain constant region having the amino acid sequence shown in SEQ ID NO: 15. In another aspect of the invention, anti-HER2 antibody-drug conjugates comprise an antibody comprising a heavy chain protein having the amino acid sequence shown in SEQ ID NO: 14 and a light chain protein having the amino acid sequence shown in SEQ ID NO: 16.

Table 1 provides the amino acid (protein) sequences and associated nucleic acid (DNA) sequences of humanized HER2 antibodies used in constructing the site-specific ADCs used in the invention. The CDRs shown are defined by Kabat numbering scheme.

The antibody heavy chains and light chains shown in Table 1 have the trastuzumab heavy chain variable region (VH) and light chain variable region (VL). The heavy chain constant region and light chain constant region are derivatized from trastuzumab and contain on or more modification to allow for site specific conjugation when making the ADCs used in the invention.

Modifications to the amino acid sequences in the antibody constant region to allow for site specific conjugation are underlined and bolded. The nomenclature for the antibodies derivatized from trastuzumab is T (for trastuzumab) and then in parenthesis the position of the amino acid of modification flanked by the single letter amino acid code for the wild type residue and the single letter amino acid code for the residue that is now in that position in the derivatized antibody. An exception to this nomenclature is “kK183C” which denotes that position 183 on the light (kappa) chain has been modified from a lysine to a cysteine.

Table 1: Sequences of humanized HER2 antibodies

SEQ ID NO.	Description	Sequence
1	Trastuzumab VH protein	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGK GLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLR AEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS
2	VH CDR1 protein	DTYIH
3	VH CDR2 protein	RIYPTNGYTRYADSVKG
4	VH CDR3 protein	WGGDGFYAMDY
5	Trastuzumab heavy chain constant region protein	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG
6	Trastuzumab heavy chain protein	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGK GLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLR AEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE

SEQ ID NO.	Description	Sequence
		VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPG
7	Trastuzumab VL protein	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYC QQHYTTPPTFGQGTKVEIK
8	VL CDR1 protein	RASQDVNTAVA
9	VL CRD2 protein	SASFLYS
10	VL CDR3 protein	QQHYTTPPT
11	Trastuzumab light chain constant region protein	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
12	Trastuzumab light chain protein	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYC QQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
13	T(K290C) heavy chain constant region protein	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT**C**P REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG
14	T(K290C) heavy chain protein	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGK GLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLR AEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT**C**PREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPG
15	T(kK183C) light chain constant region protein	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLS**C**ADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
16	T(kK183C) light chain protein	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKA PKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYC QQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV

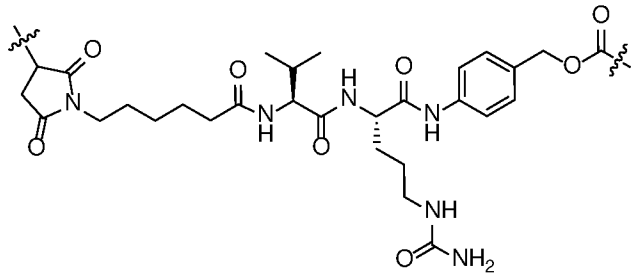
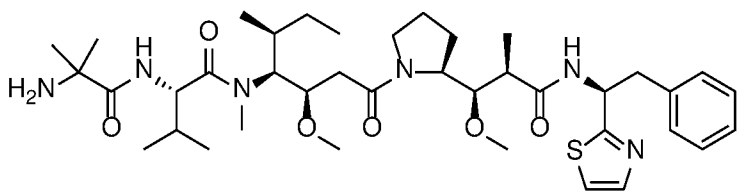
SEQ ID NO.	Description	Sequence
		CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLS**C**ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
17	Trastuzumab VH DNA	GAGGTGCAGCTGGTGGAATCCGGCGGAGGCCTGGTCCAGC CTGGCGGATCTCTGCGGCTGTCTTGCGCCGCCTCCGGCTTC AACATCAAGGACACCTACATCCACTGGGTCCGACAGGCACCT GGCAAGGGACTGGAATGGGTGGCCCGGATCTACCCCACCAA CGGCTACACCAGATACGCCGACTCCGTGAAGGGCCGGTTCA CCATCTCCGCCGACACCTCCAAGAACACCGCCTACCTGCAGA TGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGC TCCAGATGGGGAGGCGACGGCTTCTACGCCATGGACTACTG GGGCCAGGGCACCCTGGTCACCGTGTCTAGC
18	Trastuzumab heavy chain DNA	GAGGTGCAGCTGGTGGAATCCGGCGGAGGCCTGGTCCAGC CTGGCGGATCTCTGCGGCTGTCTTGCGCCGCCTCCGGCTTC AACATCAAGGACACCTACATCCACTGGGTCCGACAGGCACCT GGCAAGGGACTGGAATGGGTGGCCCGGATCTACCCCACCAA CGGCTACACCAGATACGCCGACTCCGTGAAGGGCCGGTTCA CCATCTCCGCCGACACCTCCAAGAACACCGCCTACCTGCAGA TGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGC TCCAGATGGGGAGGCGACGGCTTCTACGCCATGGACTACTG GGGCCAGGGCACCCTGGTCACCGTGTCTAGCGCGTCGACCA AGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGC ACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA CTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCG CCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAG TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAAT CACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCC CAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGC ACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGT CACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG CCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTAC CGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCT GAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT CCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA GCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGG AGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAG CAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCG TGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCA CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA TGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAG AAGAGCCTCTCCCTGTCCCCGGGT
19	Trastuzumab VL DNA	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCCGCCTCT GTGGGCGACAGAGTGACCATCACCTGTCGGGCCTCCCAGGA CGTGAACACCGCCGTGGCCTGGTATCAGCAGAAGCCCGGCA AGGCCCCCAAGCTGCTGATCTACTCCGCCTCCTTCCTGTACT CCGGCGTGCCCTCCCGGTTCTCCGGCTCCAGATCTGGCACC GACTTTACCCTGACCATCTCCAGCCTGCAGCCCGAGGACTTC

SEQ ID NO.	Description	Sequence
		GCCACCTACTACTGCCAGCAGCACTACACCACCCCCCCCACC TTTGGCCAGGGCACCAAGGTGGAAATCAAG
20	Trastuzumab light chain DNA	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCCGCCTCT GTGGGCGACAGAGTGACCATCACCTGTCGGGCCTCCCAGGA CGTGAACACCGCCGTGGCCTGGTATCAGCAGAAGCCCGGCA AGGCCCCCAAGCTGCTGATCTACTCCGCCTCCTTCCTGTACT CCGGCGTGCCCTCCCGGTTCTCCGGCTCCAGATCTGGCACC GACTTTACCCTGACCATCTCCAGCCTGCAGCCCGAGGACTTC GCCACCTACTACTGCCAGCAGCACTACACCACCCCCCCCACC TTTGGCCAGGGCACCAAGGTGGAAATCAAGCGGACCGTGGC CGCTCCCTCCGTGTTCATCTTCCCACCCTCCGACGAGCAGCT GAAGTCCGGCACCGCCTCCGTCGTGTGCCTGCTGAACAACTT CTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACG CCCTGCAGTCCGGCAACTCCCAGGAATCCGTCACCGAGCAG GACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACC CTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTG CGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGT CCTTCAACCGGGGCGAGTGC
21	T(K290C) heavy chain constant region DNA	GCGTCGACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTC CTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCC TGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGG AACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGC TGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT GACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAG AAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCA CCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTT CCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG GACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACG AAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG GAGGTGCATAATGCCAAGACATGCCCGCGGGAGGAGCAGTA CAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCA CCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCA AAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTG CCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCT GACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGT GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGA CCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCT ATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAAC CACTACACGCAGAAGAGCCTCTCCCTGTCCCCGGGT
22	T(K290C) heavy chain DNA	GAGGTGCAGCTGGTGGAATCCGGCGGAGGCCTGGTCCAGC CTGGCGGATCTCTGCGGCTGTCTTGCGCCGCCTCCGGCTTC AACATCAAGGACACCTACATCCACTGGGTCCGACAGGCACCT GGCAAGGGACTGGAATGGGTGGCCCGGATCTACCCCACCAA CGGCTACACCAGATACGCCGACTCCGTGAAGGGCCGGTTCA CCATCTCCGCCGACACCTCCAAGAACACCGCCTACCTGCAGA TGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGC TCCAGATGGGGAGGCGACGGCTTCTACGCCATGGACTACTG

SEQ ID NO.	Description	Sequence
		GGGCCAGGGCACCCTGGTCACCGTGTCTAGCGCGTCGACCA AGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGC ACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA CTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCG CCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAG TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAAT CACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCC CAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGC ACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGT CACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG CCAAGACATGCCCGCGGGAGGAGCAGTACAACAGCACGTAC CGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCT GAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT CCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA GCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGG AGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAG CAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCG TGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCA CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA TGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAG AAGAGCCTCTCCCTGTCCCCGGGT
23	T(kK183C) light chain constant region DNA	CGGACCGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCCTCC GACGAGCAGCTGAAGTCCGGCACCGCCTCCGTCGTGTGCCT GCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGA AGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAATCC GTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTC CTCCACCCTGACCCTGTCCTGCGCCGACTACGAGAAGCACAA GGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCC CCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
24	T(kK183C) light chain DNA	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCCGCCTCT GTGGGCGACAGAGTGACCATCACCTGTCGGGCCTCCCAGGA CGTGAACACCGCCGTGGCCTGGTATCAGCAGAAGCCCGGCA AGGCCCCCAAGCTGCTGATCTACTCCGCCTCCTTCCTGTACT CCGGCGTGCCCTCCCGGTTCTCCGGCTCCAGATCTGGCACC GACTTTACCCTGACCATCTCCAGCCTGCAGCCCGAGGACTTC GCCACCTACTACTGCCAGCAGCACTACACCACCCCCCCCACC TTTGGCCAGGGCACCAAGGTGGAAATCAAGCGGACCGTGGC CGCTCCCTCCGTGTTCATCTTCCCACCCTCCGACGAGCAGCT GAAGTCCGGCACCGCCTCCGTCGTGTGCCTGCTGAACAACTT CTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACG CCCTGCAGTCCGGCAACTCCCAGGAATCCGTCACCGAGCAG GACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACC CTGTCCTGCGCCGACTACGAGAAGCACAAGGTGTACGCCTG CGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGT CCTTCAACCGGGGCGAGTGC

In a particular aspect, the invention can be practiced using the anti-HER2 antibody-drug conjugate comprising an antibody designated T(kK183C+K290C), described in U.S. Patent No. 10,689,458 and International Patent Application Publication WO 2017/093844, each of which is herein incorporated by reference in its entirety. In another aspect, the invention can be practiced using the anti-HER2 antibody-drug conjugate further comprising a drug and a linker, wherein the drug is the auristatin drug 2-methylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (also known as 0101)) (Table 2 *infra*), and the linker is the cleavable linker maleimidocaproyl–valine-citrulline-p-aminobenzyloxycarbonyl (vc) (Table 2 *infra*). In a particular aspect, the invention can be practiced using the anti-HER2 antibody-drug conjugate T(kK183C+K290C)-vc0101 (see Figure 1).

Table 2: Linker & Payload

Name	Structure
maleimidocaproyl–valine-citrulline-p-aminobenzyloxycarbonyl (vc)	
2-methylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (0101)	

Pediatric Cancers

In some aspects of the invention, the HER2-expressing pediatric cancer to be treated with the site specific HER2 ADCs of the invention can express HER2 at a high, moderate or low level. In some embodiments, the cancer to be treated is resistant to, refractory to and/or relapsed from treatment with trastuzumab and/or trastuzumab emtansine (T-DM1) either of which alone or in combination with a taxane. Pediatric cancers to be treated include, but are not limited to, ependymoma, astrocytoma, glioblastoma, high grade glioma, medulloblastoma, B-cell acute lymphoblastic leukemia (B-cell ALL), atypical teratoid/rhabdoid tumor (AT/RT), neuroblastoma, osteosarcoma or sarcoma. In a more specific embodiment, the pediatric cancer is ependymoma. In another embodiment, the pediatric cancer is atypical teratoid/rhabdoid tumor (AT/RT). In another embodiment, the pediatric cancer is neuroblastoma.

Pharmaceutical Compositions

Further provided herein are pharmaceutical compositions comprising anti-HER2 ADCs disclosed herein and a pharmaceutically acceptable carrier. The present invention also provides articles of manufacture, comprising a container, a composition within the container comprising an anti-HER2 ADC, and a package insert containing instructions to administer a dose of anti-HER2 ADC.

Another aspect of the invention provides for kits containing a formulation comprising a pharmaceutical composition. The kits may comprise an anti-HER2 ADC and a pharmaceutically acceptable carrier. The kits may contain instructions for QW and/or Q3W intravenous dosing of the pharmaceutical composition for the treatment of cancer and/or a HER2-expressing cancer in which the administration of an anti-HER2 ADC is beneficial.

Combination Therapies

In some aspects of the invention, the methods described herein further include a step of treating a subject with an additional form of therapy. In some aspects, the additional form of therapy is an additional anti-cancer therapy including, but not limited to, chemotherapy, radiation, surgery, hormone therapy, and/or additional immunotherapy.

The disclosed site specific HER2 ADCs may be administered as an initial treatment, or for treatment of cancers that are unresponsive to conventional therapies. In

addition, the site specific HER2 ADCs may be used in combination with other therapies (e.g., surgical excision, radiation, additional anti-cancer drugs etc.) to thereby elicit additive or potentiated therapeutic effects and/or reduce cytotoxicity of some anti-cancer agents. Site specific HER2 ADCs of the invention may be co-administered or co-formulated with additional agents or formulated for consecutive administration with additional agents in any order.

Site specific HER2 ADCs of the invention may be used in combination with other therapeutic agents including, but not limited to, therapeutic antibodies, ADCs, immunomodulating agents, cytotoxic agents, and cytostatic agents. A cytotoxic effect refers to the depletion, elimination and/or the killing of a target cells (i.e., tumor cells). A cytotoxic agent refers to an agent that has a cytotoxic and/or cytostatic effect on a cell. A cytostatic effect refers to the inhibition of cell proliferation. A cytostatic agent refers to an agent that has a cytostatic effect on a cell, thereby inhibiting the growth and/or expansion of a specific subset of cells (i.e., tumor cells). An immunomodulating agent refers to an agent that stimulates the immune response though the production of cytokines and/or antibodies and/or modulating T cell function thereby inhibiting or reducing the growth of a subset of cells (i.e., tumor cells) either directly or indirectly by allowing another agent to be more efficacious.

For combination therapies, a site specific HER2 ADC and/or one or more additional therapeutic agents are administered within any time frame suitable for performance of the intended therapy. Thus, the single agents may be administered substantially simultaneously (i.e., as a single formulation or within minutes or hours) or consecutively in any order. For example, single agent treatments may be administered within about 1 year of each other, such as within about 10, 8, 6, 4, or 2 months, or within 4, 3, 2 or 1 week(s), or within about 5, 4, 3, 2 or 1 day(s).

The disclosed combination therapies may elicit a synergistic therapeutic effect, i.e., an effect greater than the sum of their individual effects or therapeutic outcomes. For example, a synergistic therapeutic effect may be an effect of at least about two-fold greater than the therapeutic effect elicited by a single agent, or the sum of the therapeutic effects elicited by the single agents of a given combination, or at least about five-fold greater, or at least about ten-fold greater, or at least about twenty-fold greater, or at least about fifty-fold greater, or at least about one hundred-fold greater. A synergistic therapeutic effect may also be observed as an increase in therapeutic effect of at least

10% compared to the therapeutic effect elicited by a single agent, or the sum of the therapeutic effects elicited by the single agents of a given combination, or at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 60%, or at least 70%, or at least 80%, or at least 90%, or at least 100%, or more. A synergistic effect is also an effect that permits reduced dosing of therapeutic agents when they are used in combination.

For example, combination therapies encompassed by this invention include, but are not limited to, combination with SOC for treating pediatric cancers.

Examples

The following examples are meant to illustrate the methods and materials of the present invention. Suitable modifications and adaptations of the described conditions and parameters normally encountered in the art that are obvious to those skilled in the art are within the spirit and scope of the present invention.

Example 1

Dosage Forms, Packaging and Administration of T(kK183C+K290C)-vc0101 ADC

T(kK183C+K290C)-vc0101 ADC

T(kK183C+K290C)-vc0101 ADC is presented as a powder for reconstitution and IV administration. Each vial contains 40 mg of T(kK183C+K290C)-vc0101 ADC , is sealed with a coated stopper and an overseal, and is labeled according to local regulatory requirements.

T(kK183C+K290C)-vc0101 ADC will be administered on Day 1 of each 21 day cycle. A cycle is defined as the time from Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 21 days. In addition, alternative dosing schedules may be evaluated.

T(kK183C+K290C)-vc0101 ADC will be administered intravenously over approximately 60 minutes (±15 minutes) on an outpatient basis.

The decision to incorporate pre-medication in all patients will be made following discussions between the sponsor and the investigators. Patients should be pre-treated with acetaminophen and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before each PF-06804103 administration.

Suggested starting doses are 650 mg to 1000 mg acetaminophen and 50 mg diphenhydramine (or equivalent of other antihistamine) IV or oral. Two additional doses of acetaminophen may be administered approximately every 4-6 hours after the initial pre-treatment or as needed

Example 2

T(kK183C+K290C)-vc0101 ADC (PF-06804103) To Treat HER2 Positive Ependymoma in Pediatric Patients

Brain tumors remain a leading cause of cancer-related deaths in children. Ependymoma is the third most common pediatric brain tumor with treatment remaining surgery and radiation. The cell surface marker HER2 is highly expressed on the vast majority of ependymomas spanning location and molecular subgroup. Accordingly, HER2 serves as a rationale target of HER2-ADC therapy for treatment of ependymoma.

In vitro and in vivo assays will be performed to evaluate efficacy and tumor penetration of T(kK183C+K290C)-vc0101 ADC to treat ependymoma in pediatric patients.

WHAT IS CLAIMED IS:

1. An anti-HER2 antibody-drug conjugate for use in the treatment of a pediatric cancer and/or HER2-expressing pediatric cancer in a patient, wherein the anti-HER2 antibody-drug conjugate is administrable or administered at least twice every week, at least weekly (QW), at least every 2 weeks (Q2W), at least every 3 weeks (Q3W) or at least every 4 weeks (Q4W).

2. The anti-HER2 antibody-drug conjugate for use of claim 1, wherein the anti-HER2 antibody-drug conjugate is administrable or administered every 3 weeks (Q3W).

3. The anti-HER2 antibody-drug conjugate for use of claim 1 or 2, wherein the anti-HER2 antibody-drug conjugate is administrable or administered at a dose of about 0.010 mg/kg to about 10 mg/kg, about 0.010 mg/kg to about 5 mg/kg, about 0.10 mg/kg to about 1 mg/kg or about 0.10 mg/kg to about 0.50 mg/kg.

4. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 3, wherein the anti-HER2 antibody-drug conjugate is administrable or administered at a dose of at least 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.95, 1.00, 1.10, 1.20, 1.30, 1.40, 1.50, 2.00, 2.50, 2.70, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00 mg/kg.

5. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 4, wherein the anti-HER2 antibody-drug conjugate is administrable or administered at a dose of about 0.15 mg/kg, 0.50 mg/kg, 1.20 mg/kg, 2.00 mg/kg, 2.70 mg/kg, 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg.

6. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 5, wherein the anti-HER2 antibody-drug conjugate is administrable or administered every 3 weeks (Q3W) at a dose of about 0.15 mg/kg, 0.50 mg/kg, 1.20 mg/kg, 2.00 mg/kg, 2.70 mg/kg, 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg.

7. The anti-HER2 antibody-drug conjugate for use of claim 6, wherein the anti-HER2 antibody-drug conjugate is administrable or administered every 3 weeks (Q3W) at a dose of about 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg.

8. The anti-HER2 antibody-drug conjugate for use of claim 7, wherein the anti-HER2 antibody-drug conjugate is administrable every 3 weeks (Q3W) at a dose of about 4.00 mg/kg mg/kg.

9. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 8, wherein the anti-HER2 antibody-drug conjugate is administrable or administered intravenously, subcutaneously, intramuscularly, by bolus injection, intracerebrally, intracranially or by sustained release.

10. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 9, wherein the anti-HER2 antibody-drug conjugate is formulated in a pharmaceutical composition.

11. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 10, wherein the antibody comprises a VH CDR1 having the amino acid sequence shown in SEQ ID NO: 2, VH CDR2 having the amino acid sequence shown in SEQ ID NO: 3, and VH CDR3 having the amino acid sequence shown in SEQ ID NO: 4, and/or VL CDR1 having the amino acid sequence shown in SEQ ID NO: 8, VL CDR2 having the amino acid sequence shown in SEQ ID NO: 9, and VL CDR3 having the amino acid sequence shown in SEQ ID NO: 10.

12. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 11, wherein the anti-HER2 antibody-drug conjugate comprises an antibody having three CDRS from a heavy chain protein having the amino acid sequence shown in SEQ ID NO: 14 and three CDRS from a light chain protein having the amino acid sequence shown in SEQ ID NO: 16.

13. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 12, wherein the antibody is T(kK183C+K290C).

14. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 13, wherein the anti-HER2 antibody-drug conjugate further comprises a drug and a linker.

15. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 14, wherein the drug is 2-methylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (0101) and the linker is maleimidocaproyl–valine-citrulline-p-aminobenzyloxycarbonyl (vc).

16. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 15, wherein the anti-HER2 antibody-drug conjugate is T(kK183C+K290C)-vc0101.

17. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 16, wherein the pediatric cancer and/or HER2-expressing pediatric cancer is characterized by overexpression of HER2.

18. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 17, wherein the pediatric cancer or HER2-expressing pediatric cancer is ependymoma, astrocytoma, glioblastoma, high grade glioma, medulloblastoma, B-cell acute lymphoblastic leukemia (B-cell ALL), atypical teratoid/rhabdoid tumor (AT/RT), neuroblastoma, osteosarcoma or sarcoma.

19. The anti-HER2 antibody-drug conjugate for use of claim 18, wherein the cancer is ependymoma.

20. The anti-HER2 antibody-drug conjugate for use of claim 18, wherein the cancer is atypical teratoid/rhabdoid tumor (AT/RT).

21. The anti-HER2 antibody-drug conjugate for use of claim 18, wherein the cancer is neuroblastoma.

22. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 21, wherein the treatment results in a decrease in tumor size of at least 1%, at least 5%,

at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or 100% as compared to the tumor size in the patient prior to first administration of the anti-HER2 antibody-drug conjugate.

23. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 22, wherein the treatment is an initial treatment.

24. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 22, wherein the cancer and/or HER2-expressing cancer is unresponsive to conventional therapies.

25. The anti-HER2 antibody-drug conjugate for use of any one of claims 1 to 24, wherein the patient is an infant, child or adolescent.

26. A method for the treatment of a patient having a pediatric cancer and/or an HER2-expressing pediatric cancer, comprising administering to the patient an effective amount of an anti-HER2 antibody-drug conjugate (ADC) at least twice every week, at least weekly (QW), at least every 2 weeks (Q2W), at least every 3 weeks (Q3W) or at least every 4 weeks (Q4W).

27. The method of claim 26, wherein the anti-HER2 antibody-drug conjugate is administered every 3 weeks (Q3W).

28. The method of claim 26 or 27, wherein the anti-HER2 antibody-drug conjugate is administered at a dose of about 0.010 mg/kg to about 10 mg/kg, about 0.010 mg/kg to about 5 mg/kg, about 0.10 mg/kg to about 1 mg/kg or about 0.10 mg/kg to about 0.50 mg/kg.

29. The method of any one of claims 26 to 28, wherein the anti-HER2 antibody-drug conjugate is administered at a dose of at least 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.95, 1.00, 1.10, 1.20, 1.30, 1.40, 1.50, 2.00, 2.50, 2.70, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00 mg/kg.

30. The method of any one of claims 26 to 29, wherein the anti-HER2 antibody-drug conjugate is administered at a dose of about 0.15 mg/kg, 0.50 mg/kg, 1.20 mg/kg, 2.00 mg/kg, 2.70 mg/kg, 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg.

31. The method of any one of claims 26 to 30, wherein the anti-HER2 antibody-drug conjugate is administered every 3 weeks (Q3W) at a dose of about 0.15 mg/kg, 0.50 mg/kg, 1.20 mg/kg, 2.00 mg/kg, 2.70 mg/kg, 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg.

32. The method of claim 31, wherein the anti-HER2 antibody-drug conjugate is administrable every 3 weeks (Q3W) at a dose of about 3.00 mg/kg, 4.00 mg/kg, 5.00 mg/kg, or 6.00 mg/kg.

33. The method of claim 32, wherein the anti-HER2 antibody-drug conjugate is administrable every 3 weeks (Q3W) at a dose of about 4.00 mg/kg mg/kg.

34. The method of any one of claims 26-33, wherein the anti-HER2 antibody-drug conjugate is administered intravenously, subcutaneously, intramuscularly, by bolus injection, intracerebrally, intracranially or by sustained release.

35. The method of any one of claims 26 to 34, wherein the anti-HER2 antibody-drug conjugate is formulated in a pharmaceutical composition.

36. The method of any one of claims 26 to 35, wherein the antibody comprises a VH CDR1 having the amino acid sequence shown in SEQ ID NO: 2, VH CDR2 having the amino acid sequence shown in SEQ ID NO: 3, and VH CDR3 having the amino acid sequence shown in SEQ ID NO: 4, and/or VL CDR1 having the amino acid sequence shown in SEQ ID NO: 8, VL CDR2 having the amino acid sequence shown in SEQ ID NO: 9, and VL CDR3 having the amino acid sequence shown in SEQ ID NO: 10.

37. The method of any one of claims 26 to 36, wherein the anti-HER2 antibody-drug conjugate comprises an antibody having a heavy chain protein having the amino acid sequence shown in SEQ ID NO: 14 and a light chain protein having the amino acid sequence shown in SEQ ID NO: 16.

38. The method any one of claims 26 to 37, wherein the antibody is T(kK183C+K290C).

39. The method of any one of claims 26 to 38, wherein the anti-HER2 antibody-drug conjugate further comprises a drug and a linker.

40. The method of any one of claims 26 to 39, wherein the drug is 2-methylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (0101) and the linker is maleimidocaproyl–valine-citrulline-p-aminobenzyloxycarbonyl (vc).

41. The method any one of claims 26 to 40, wherein the anti-HER2 antibody-drug conjugate is T(kK183C+K290C)-vc0101.

42. The method of any one of claims 26 to 41, wherein the pediatric cancer and/or HER2-expressing pediatric cancer is characterized by overexpression of HER2.

43. The method of any one of claims 26 to 42, wherein the pediatric cancer or HER2-expressing pediatric cancer is ependymoma, astrocytoma, glioblastoma, high grade glioma, medulloblastoma, B-cell acute lymphoblastic leukemia (B-cell ALL), atypical teratoid/rhabdoid tumor (AT/RT), neuroblastoma, osteosarcoma or sarcoma.

44. The method of claim 43, wherein the pediatric cancer is ependymoma.

45. The method of claim 43, wherein the pediatric cancer is atypical teratoid/rhabdoid tumor (AT/RT).

46. The method of claim 43, wherein the pediatric cancer isneuroblastoma.

47. The method of any one of claims 26 to 46, wherein the treatment results in a decrease in tumor size of at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%,

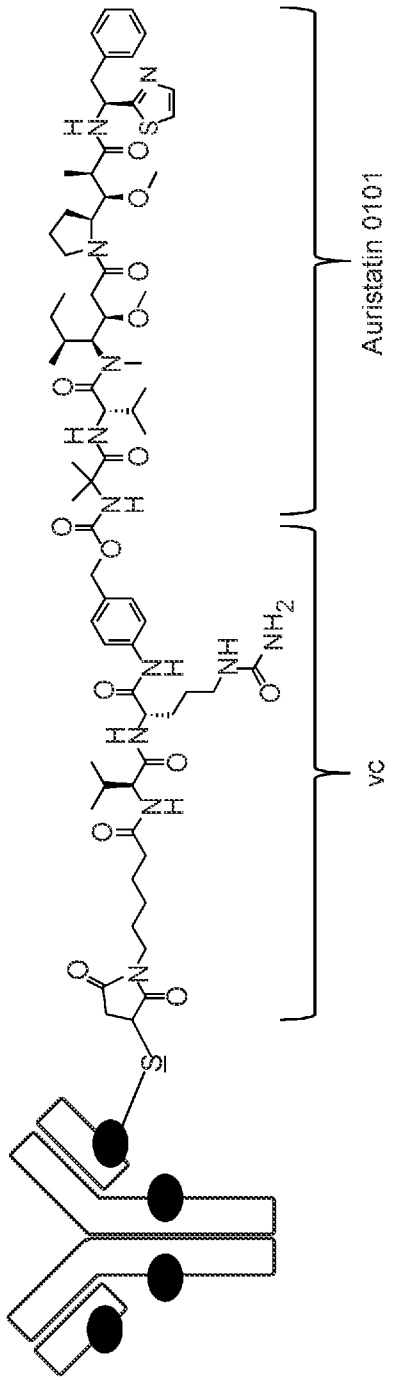
at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or 100% as compared to the tumor size in the patient prior to first administration of the anti-HER2 antibody-drug conjugate.

48. The method of any one of claims 26 to 47, wherein the treatment is an initial treatment.

49. The method of any one of claims 26 to 47, wherein the pediatric cancer and/or HER2-expressing pediatric cancer is unresponsive to conventional therapies.

50. The method of any one of claims 26 to 49, wherein the patient is an infant, child or adolescent.

Fig. 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/057027

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/68 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HINGORANI P ET AL: "Preclinical evaluation of trastuzumab deruxtecan (T-DXd; DS-8201a), a HER2 antibody-drug conjugate, in pediatric solid tumors by the Pediatric Preclinical Testing Consortium (PPTC)", CANCER RESEARCH 20200801 AMERICAN ASSOCIATION FOR CANCER RESEARCH INC. NLD, vol. 80, no. 16 SUPPL, 1 August 2020 (2020-08-01), XP009530584, ISSN: 1538-7445	1-14, 17-39, 42-50
Y	the whole document	1-50
Y	WO 2017/093844 A1 (PFIZER [US]) 8 June 2017 (2017-06-08) examples 1-20 figure 1 page 71, line 17 - page 72, line 4 page 70, line 10 - line 31	1-50

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2021	25/10/2021

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/057027

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/057027

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