[Patent Document 9] WO2006/109592

[Non-patent Documents]

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[Non-patent Document 3] Drug Des Devel Ther (2009) 3, 7-16
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[Non-patent Document 17] Proc Natl Acad Sci USA (1986) 83 (5), 1453-7
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[Non-patent Document 25] Nature Biotechnology. (1998) vol.16, p.677-681
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Summary ~~of the Invention~~

[Problems to be Solved by the Invention]

The present ~~invention~~ disclosure was achieved in view of the above circumstances. An objective of the present ~~invention~~disclosure is to provide anticancer agents comprising as an active ingredient multispecific antigen-binding molecules that bring T cells close to the target cancer cells, and can

treat cancer through the cytotoxic activity of T cells against target cancer tissues containing glypican 3-expressing cells, and are molecular forms that can be produced with high efficiency. Another objective of the present ~~invention~~disclosures is to provide combination therapies using the multispecific antigen-binding molecules and other pharmaceutical agents.

[Means for Solving the Problems]

The present inventors discovered an L chain common to a domain comprising a glypican 3-binding antibody variable region, and a domain comprising a T-cell receptor complex-binding antibody variable region, where the common L chain is capable of improving affinity to both antigens. This allows preparation of molecular forms that can be produced with high efficiency, and further discovery of novel multispecific antigen-binding molecules that maintain the strong antitumor activity possessed by T-cell redirecting antibodies such as BiTE and the excellent safety property of not inducing a cytokine storm in a cancer antigen-independent manner, and also have long half-lives in blood. Furthermore, the present inventors discovered that the multispecific antigen-binding molecules comprising common L chains target glypican 3-expressing cancer cells and cause cytotoxicity. Based on this discovery, the present inventors elucidated that the multispecific antigen-binding molecules of the present ~~invention~~disclosure cause injury to cancer tissues containing glypican 3-expressing cancer cells. The present inventors revealed anticancer agents that comprise as an active ingredient the multispecific antigen-binding molecule; methods for treating or preventing cancer by combined use of the multispecific antigen-binding molecule and another anticancer agent; multispecific antigen-binding molecules, anticancer agents, or pharmaceutical compositions comprising a combination of a multispecific antigen-binding molecule and an anticancer agent, each of which is used in combination therapies.

Specifically, the present ~~invention~~disclosure provides the following:

In one aspect, the present disclosure refers to use of a pharmaceutical composition in the manufacture of a medicament for treating a glypican 3-positive cancer or for preventing a glypican 3-positve cancer, wherein the pharmaceutical composition is to be used in combination with an immune checkpoint inhibitor or an angiogenic inhibitor, wherein the pharmaceutical composition comprising as an active ingredient a bispecific antibody of any one of the bispecific antibodies below that comprise an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity: (1) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 211, respectively; CDR1, CDR2, and CDR3 comprised in an antibody

H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 142, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively; (2) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 211, respectively; CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 144, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively; (3) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 144, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively; (4) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 142, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively; and (5) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 168, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively; wherein the immune checkpoint inhibitor is an anti-CTLA-4 antibody, Pembrolizumab, Nivolumab, MEDI0680, PDR001, BGB-A317, REGN2810, SHR-1210, PF-06801591, Atezolizumab, Avelumab, Durvalumab, MDX-1105,

Ipilimumab, Tremelimumab, MBG452, BMS-986016 or LAG525, and wherein the angiogenic inhibitor is Bevacizumab, Sorafenib, Everolimus or Temsirolimus.

In another aspect, the present disclosure refers to use of a pharmaceutical composition in the manufacture of a medicament for treating a glypican 3-positive cancer or for preventing a glypican 3-positive cancer, wherein the pharmaceutical composition is to be used in combination with an immune checkpoint inhibitor or an angiogenic inhibitor, wherein the pharmaceutical composition comprises as an active ingredient a bispecific antibody of any one of the bispecific antibodies below: (1) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 211; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 142; and a variable region of a common L chain is the amino acid sequence of SEQ ID NO: 223; (2) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 211; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 144; and a variable region of a common L chain is the amino acid sequence of SEQ ID NO: 223; (3) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 206; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 144; and a variable region of a common L chain is the amino acid sequence of SEQ ID NO: 223; (4) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 206; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 142; and a variable region of a common L chain Is the amino acid sequence of SEQ ID NO: 223; and (5) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 206; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 168; and a variable region of a common L chain is the amino acid sequence of SEQ ID NO: 223; wherein the immune checkpoint inhibitor is an anti-CTLA-4 antibody, Pembrolizumab, Nivolumab, MEDI0680, PDR001, BGB-A317, REGN2810, SHR-1210, PF-06801591, Atezolizumab, Avelumab, Durvalumab, MDX-1105, Ipilimumab, Tremelimumab, MBG452, BMS-986016 or LAG525, and wherein the angiogenic inhibitor is Bevacizumab, Sorafenib, Everolimus or Temsirolimus.

In another aspect, the present disclosure refers to use of a pharmaceutical composition in the manufacture of a medicament for treating a glypican 3-positive cancer or for preventing a glypican 3-positive cancer, wherein the pharmaceutical composition is to be used in combination with an immune checkpoint inhibitor or an angiogenic inhibitor, wherein the pharmaceutical composition comprises as an active ingredient a bispecific antibody of any one of the bispecific

antibodies below: (1) a bispecific antibody that has the antibody H chain of SEQ ID NO: 386 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 398 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410; (2) a bispecific antibody that has the antibody H chain of SEQ ID NO: 386 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 399 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410; (3) a bispecific antibody that has the antibody H chain of SEQ ID NO: 385 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 399 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410; (4) a bispecific antibody that has the antibody H chain of SEQ ID NO: 385 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 398 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410; and (5) a bispecific antibody that has the antibody H chain of SEQ ID NO: 385 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 402 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410; wherein the immune checkpoint inhibitor is an anti-CTLA-4 antibody, Pembrolizumab, Nivolumab, MEDI0680, PDR001, BGB-A317, REGN2810, SHR-1210, PF-06801591, Atezolizumab, Avelumab, Durvalumab, MDX-1105, Ipilimumab, Tremelimumab, MBG452, BMS-986016 or LAG525, and wherein the angiogenic inhibitor is Bevacizumab, Sorafenib, Everolimus or Temsirolimus.

[1] An anticancer agent comprising as an active ingredient a bispecific antibody of any one of (a) to (c) below that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity:

(a) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in the antibody variable region having glypican 3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in the antibody variable region having CD3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 168, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are sequences

antibody.

[16] An agent for inducing cytotoxicity, an agent for suppressing cell proliferation, an agent for inhibiting cell proliferation, an agent for activating immune response, an agent for treating cancer, or an agent for preventing cancer, which comprises the pharmaceutical composition of any one of [7] to [15].

[17] The anticancer agent of [1], wherein CDR1, CDR2, and CDR3 are CDR1, CDR2, and CDR3 regions based on Kabat numbering.

The following ~~invention~~disclosures are also provided:

[2-1] An anticancer agent comprising as an active ingredient a multispecific antigen-binding molecule that comprises:

(1) a domain comprising an antibody variable region having glypican 3-binding activity,

(2) a domain comprising an antibody variable region having T-cell receptor complex-binding activity, and

(3) a domain comprising an Fc region with reduced binding activity towards an Fcγ receptor, wherein the L chain variable regions comprised in the variable region of (1) and the variable region of (2) have a common amino acid sequence; wherein the multispecific antigen-binding molecule has a cytotoxic activity equivalent to or greater than that of the bispecific antibody GPC3_ERY22_rCE115 comprising a glypican 3-binding domain comprising SEQ ID NOs: 47 and 48, and a T-cell receptor complex-binding domain comprising SEQ ID NOs: 49 and 50.

[2-2] The anticancer agent of [2-1], wherein the cytotoxic activity is T-cell-dependent cytotoxic activity.

[2-3] The anticancer agent of [2-1] or [2-2], wherein the T-cell receptor complex-binding activity is binding activity towards a T-cell receptor.

[2-4] The anticancer agent of any one of [2-1] to [2-3], wherein the T-cell receptor complex-binding activity is binding activity towards a CD3ε chain.

[2-5] The anticancer agent of any one of [2-1] to [2-4], wherein the antibody variable region of (1) in [1] is an antibody variable region that comprises any one of the combinations of H-chain CDR1, CDR2, and CDR3 selected from (a1) to (a5) below, or an antibody variable region functionally equivalent thereto:

(a1) CDR1, CDR2, and CDR3 identical to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 40;

(a2) CDR1, CDR2, and CDR3 identical to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 197;

(a3) CDR1, CDR2, and CDR3 identical to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206;

variable region having the amino acid sequence of SEQ ID NO: 164 and a constant region having the amino acid sequence of SEQ ID NO: 60 or 62; and a common antibody L chain having the amino acid sequence of SEQ ID NO: 223; and

(h25) a bispecific antibody having an antibody H chain having glypican 3-binding activity that comprises an antibody H-chain variable region having the amino acid sequence of SEQ ID NO: 211 and a constant region having the amino acid sequence of SEQ ID NO: 61; an antibody H chain having T-cell receptor complex-binding activity that comprises an antibody H-chain variable region having the amino acid sequence of SEQ ID NO: 168 and a constant region having the amino acid sequence of SEQ ID NO: 60 or 62; and a common antibody L chain having the amino acid sequence of SEQ ID NO: 223.

Furthermore, the present ~~invention~~disclosure relates to an anticancer agent comprising as an active ingredient a multispecific antigen-binding molecule which comprises the following domains:

(3-1) a domain comprising an antibody variable region having glypican 3-binding activity;

(3-2) a domain comprising an antibody variable region having T-cell receptor complex-binding activity;

wherein the L-chain variable regions contained in the variable regions of (3-1) and (3-2) have a commonly shared amino acid sequence. The present ~~invention~~disclosure also relates to an anticancer agent comprising as an active ingredient the domain of (3-1), which is more specifically a domain that comprises antibody heavy-chain and/or light-chain variable regions having glypican 3-binding activity, and which is comprised in the multispecific antigen-binding molecule. The present ~~invention~~disclosure additionally relates to an anticancer agent comprising as an active ingredient the domain of (3-2), which is more specifically a domain that comprises an antibody variable region having T-cell receptor complex-binding activity, and which is comprised in the multispecific antigen-binding molecule. Details of the domains of (3-1) and (3-2) may include those described in [2-1] to [2-22] mentioned above. The multispecific antigen-binding molecule may be a bispecific antibody. Furthermore, the multispecific antigen-binding molecule may further comprise a domain comprising an Fc region, and the Fc region may have a reduced Fcγ receptor-binding activity. Details of the domain comprising an Fc region may include those described in [2-1] to [2-22] mentioned above. Furthermore, the present ~~invention~~disclosure relates to an anticancer agent comprising the multispecific antigen-binding molecule and a pharmaceutically acceptable carrier. The anticancer agent may induce cytotoxicity, the cytotoxicity may be T-cell-dependent cellular cytotoxicity, and the agent may be for administration to a patient in need of the multispecific antigen-binding molecule.

The present ~~invention~~disclosure also provides an anticancer agent comprising as an active ingredient a multispecific antigen-binding molecule that binds to epitopes overlapping and/or

competing with epitopes on each of glypican 3 and T-cell receptor complex bound by the multispecific antigen-binding molecule of any one of (e1) to (e25) of [2-14] mentioned above, and a multispecific antigen-binding molecule that binds to epitopes overlapping and/or competing with epitopes on each of glypican 3 and T-cell receptor complex bound by the multispecific antigen-binding molecule of any one of (f1) to (f25) of [2-15].

Regarding (g1) and (g2) of [2-20] mentioned above, of the two Fc regions, the former Fc region may be included in the antibody H chain having glypican 3-binding activity and the latter Fc region may be included in the antibody H chain having T-cell receptor complex-binding activity; or the former Fc region may be included in the antibody H chain having T-cell receptor complex-binding activity and the latter Fc region may be included in the antibody H chain having glypican 3-binding activity.

The present ~~invention~~disclosure also provides anticancer agents comprising as an active ingredient a bispecific antibody that binds to epitopes overlapping and/or competing with epitopes on each of glypican 3 and T-cell receptor complex bound by a bispecific antibody which has the antibody H chain of SEQ ID NO: 385 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 402 having CD3-binding activity, and the common antibody L chains of SEQ ID NO: 410.

The following ~~invention~~disclosures are also provided:

[4-1] A pharmaceutical composition comprising another anticancer agent as an active ingredient, the pharmaceutical composition being used in combination with a bispecific antibody of any one of (a) to (c) below:

(a) a bispecific antibody that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity, wherein CDR1, CDR2, and CDR3 comprised in the antibody variable region having glypican 3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in the antibody variable region having CD3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 168, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;

(b) a bispecific antibody that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity, wherein the antibody variable region having glypican 3-binding activity is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 206; the antibody variable region having CD3-binding

antibody has an antibody H chain having glypican 3-binding activity and having at least 80% identity to the amino acid sequence of SEQ ID NO: 385; an antibody H chain having CD3-binding activity and having at least 80% identity to the amino acid sequence of SEQ ID NO: 402; and antibody common L chains having at least 80% identity to the amino acid sequence of SEQ ID NO: 410.

[4-5] The pharmaceutical composition of [4-4], which is a combination preparation.

[4-6] The pharmaceutical composition of [4-4], wherein the bispecific antibody and said another anticancer agent are administered separately.

[4-7] The pharmaceutical composition of [4-6], wherein the bispecific antibody and said another anticancer agent are administered simultaneously or sequentially.

[4-8] The pharmaceutical composition of any one of [4-1] to [4-7], wherein said another anticancer agent is a chemotherapeutic agent, a T cell-activating agonist agent, an immune checkpoint inhibitor, or an angiogenic inhibitor.

[4-9] The pharmaceutical composition of any one of [4-1] to [4-8], which is for treating or preventing any cancer selected from the group consisting of gastric cancer, head and neck cancer, esophageal cancer, lung cancer, liver cancer, ovary cancer, breast cancer, colon cancer, kidney cancer, skin cancer, muscle tumor, pancreas cancer, prostate cancer, testis cancer, uterine cancer, cholangiocarcinoma, Merkel cell carcinoma, bladder cancer, thyroid cancer, schwannoma, adrenal cancer, anus cancer, central nervous system tumor, neuroendocrine tissue tumor, penis cancer, pleura tumor, salivary gland tumor, vulva cancer, thymoma, and childhood cancer.

[4-10] An agent for inducing cytotoxicity, an agent for suppressing cell proliferation, an agent for inhibiting cell proliferation, an agent for activating immune response, an agent for treating cancer, or an agent for preventing cancer, which comprises the pharmaceutical composition of any one of [4-1] to [4-9].

The following ~~invention~~disclosures are also provided:

[4-11] A combination of a bispecific antibody of any one of (a) to (c) below and another anticancer agent:

(a) a bispecific antibody that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity, wherein CDR1, CDR2, and CDR3 comprised in the antibody variable region having glypican 3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in the antibody variable region having CD3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 168, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are sequences having at least 80% identity to the

amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;

(b) a bispecific antibody that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity, wherein the antibody variable region having glypican 3-binding activity is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 206; the antibody variable region having CD3-binding activity is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 168; and an antibody variable region of a common L chain is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 223; and

(c) a bispecific antibody that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity, wherein the bispecific antibody has an antibody H chain having glypican 3-binding activity and having at least 80% identity to the amino acid sequence of SEQ ID NO: 385; an antibody H chain having CD3-binding activity and having at least 80% identity to the amino acid sequence of SEQ ID NO: 402; and antibody common L chains having at least 80% identity to the amino acid sequence of SEQ ID NO: 410.

[4-12] The combination of [4-11], wherein the bispecific antibody is administered simultaneously with said another anticancer agent.

[4-13] The combination of [4-11], wherein the bispecific antibody is administered before or after administration of said another anticancer agent.

[4-14] The combination of any one of [4-11] to [4-13], wherein said another anticancer agent is a chemotherapeutic agent, a T cell-activating agonist agent, an immune checkpoint inhibitor, or an angiogenic inhibitor.

[4-15] The combination of any one of [4-11] to [4-14], which is for treating or preventing any cancer selected from the group consisting of gastric cancer, head and neck cancer, esophageal cancer, lung cancer, liver cancer, ovary cancer, breast cancer, colon cancer, kidney cancer, skin cancer, muscle tumor, pancreas cancer, prostate cancer, testis cancer, uterine cancer, cholangiocarcinoma, Merkel cell carcinoma, bladder cancer, thyroid cancer, schwannoma, adrenal cancer, anus cancer, central nervous system tumor, neuroendocrine tissue tumor, penis cancer, pleura tumor, salivary gland tumor, vulva cancer, thymoma, and childhood cancer.

[4-16] An agent for inducing cytotoxicity, an agent for suppressing cell proliferation, an agent for inhibiting cell proliferation, an agent for activating immune response, an agent for treating cancer, or an agent for preventing cancer, which comprises the combination of any one of [4-11] to [4-15].

The following ~~invention~~disclosures are also provided:

[4-17] A method for inducing cytotoxicity, for suppressing cell proliferation, for inhibiting cell

[4-22] The method of any one of [4-17] to [4-21], wherein the bispecific antibody and said another anticancer agent are administrated separately.

[4-23] The method of any one of [4-17] to [4-22], wherein the bispecific antibody and said another anticancer agent are administrated simultaneously or sequentially.

[4-24] The method of any one of [4-17] to [4-23], wherein said another anticancer agent is a chemotherapeutic agent, a T cell-activating agonist agent, an immune checkpoint inhibitor, or an angiogenic inhibitor.

[4-25] The method of any one of [4-17] to [4-24], wherein the cancer is any cancer selected from the group consisting of gastric cancer, head and neck cancer, esophageal cancer, lung cancer, liver cancer, ovary cancer, breast cancer, colon cancer, kidney cancer, skin cancer, muscle tumor, pancreas cancer, prostate cancer, testis cancer, uterine cancer, cholangiocarcinoma, Merkel cell carcinoma, bladder cancer, thyroid cancer, schwannoma, adrenal cancer, anus cancer, central nervous system tumor, neuroendocrine tissue tumor, penis cancer, pleura tumor, salivary gland tumor, vulva cancer, thymoma, and childhood cancer.

The following ~~invention~~disclosures are also provided:

[4-26] A kit comprising:

(A) a pharmaceutical composition comprising a bispecific antibody of any one of (a) to (c) below;

(B) a container; and

(C) an instruction or a label indicating that the bispecific antibody and at least one type of another anticancer agent are administered in combination to an individual for treating or preventing cancer in the individual;

(a) a bispecific antibody that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity, wherein CDR1, CDR2, and CDR3 comprised in the antibody variable region having glypican 3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in the antibody variable region having CD3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 168, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;

(b) a bispecific antibody that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity, wherein the antibody variable region having glypican 3-binding activity is a sequence having at least 80% identity to

[4-29] The kit of any one of [4-26] to [4-28], wherein the bispecific antibody is administered simultaneously with said another anticancer agent.

[4-30] The kit of any one of [4-26] to [4-28], wherein the bispecific antibody is administered before or after administration of said another anticancer agent.

[4-31] The kit of any one of [4-26] to [4-30], wherein said another anticancer agent is a chemotherapeutic agent, a T cell-activating agonist agent, an immune checkpoint inhibitor, or an angiogenic inhibitor.

[4-32] The kit of any one of [4-26] to [4-31], wherein the cancer is any cancer selected from the group consisting of gastric cancer, head and neck cancer, esophageal cancer, lung cancer, liver cancer, ovary cancer, breast cancer, colon cancer, kidney cancer, skin cancer, muscle tumor, pancreas cancer, prostate cancer, testis cancer, uterine cancer, cholangiocarcinoma, Merkel cell carcinoma, bladder cancer, thyroid cancer, schwannoma, adrenal cancer, anus cancer, central nervous system tumor, neuroendocrine tissue tumor, penis cancer, pleura tumor, salivary gland tumor, vulva cancer, thymoma, and childhood cancer.

The following ~~invention~~disclosures are also provided:

[4-33] A method for inducing damage to a cancer cell or a cancer cell-comprising tumor tissue, or a method for suppressing proliferation of a cancer cell or growth of a cancer cell-comprising tumor tissue, by contacting a cancer cell with a bispecific antibody of any one of (a) to (c) below and another anticancer agent;

(a) a bispecific antibody that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity, wherein CDR1, CDR2, and CDR3 comprised in the antibody variable region having glypican 3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in the antibody variable region having CD3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 168, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;

(b) a bispecific antibody that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity, wherein the antibody variable region having glypican 3-binding activity is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 206; the antibody variable region having CD3-binding activity is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 168; and an antibody variable region of a common L chain is a sequence having at least 80%

sequence of SEQ ID NO: 410.

[4-35] The method of [4-33] or [4-34], wherein said another anticancer agent is a chemotherapeutic agent, a T cell-activating agonist agent, an immune checkpoint inhibitor, or an angiogenic inhibitor.

[4-36] The method of any one of [4-33] to [4-35], wherein the cancer cell is any cancer cell selected from the group consisting of gastric cancer, head and neck cancer, esophageal cancer, lung cancer, liver cancer, ovary cancer, breast cancer, colon cancer, kidney cancer, skin cancer, muscle tumor, pancreas cancer, prostate cancer, testis cancer, uterine cancer, cholangiocarcinoma, Merkel cell carcinoma, bladder cancer, thyroid cancer, schwannoma, adrenal cancer, anus cancer, central nervous system tumor, neuroendocrine tissue tumor, penis cancer, pleura tumor, salivary gland tumor, vulva cancer, thymoma, and childhood cancer.

The following ~~invention~~disclosures are also provided:

[5-1] The pharmaceutical composition of any one of [7] to [12] and [4-1] to [4-9], which is for increasing and/or maintaining the expression of CD3ε chain in an individual as compared to administration of the bispecific antibody of any one of [7] (a) to (c) or said another anticancer agent alone.

[5-2] The pharmaceutical composition of any one of [7] to [12] and [4-1] to [4-9], which is for expanding T cell population in an individual as compared to administration of the bispecific antibody of any one of [7] (a) to (c) or said another anticancer agent alone.

[5-3] The pharmaceutical composition of [5-2], wherein the T cell population is an activated T cell population.

[5-4] The pharmaceutical composition of any one of [7] to [12] and [4-1] to [4-9], which is for increasing the expression of a cytokine and/or chemokine in an individual as compared to administration of the bispecific antibody of any one of [7] (a) to (c) or said another anticancer agent alone.

[5-5] The pharmaceutical composition of [5-4], wherein the cytokine and/or chemokine is one or more cytokines and/or chemokines selected from the group consisting of IFNγ, IL2, IL6, IL7, IL8, IL10, IL17A, TNF, CXCL9, and CXCL10.

[5-6] The pharmaceutical composition of any one of [7] to [12] and [4-1] to [4-9], which is for increasing the expression of a gene involved in cell death in an individual as compared to administration of the bispecific antibody of any one of [7] (a) to (c) or said another anticancer agent alone.

[5-7] The pharmaceutical composition of [5-6], wherein the gene involved in cell death is one or more genes selected from the group consisting of TNFSF10, FAS, FASL, caspase 8, and caspase 7.

[5-8] The pharmaceutical composition of any one of [7] to [12] and [4-1] to [4-9], which is for

inhibiting a gene involved in cell cycle promotion in an individual as compared to administration of the bispecific antibody of any one of [7] (a) to (c) or said another anticancer agent alone.

[5-9] The pharmaceutical composition of [5-8], wherein the gene involved in cell cycle promotion is one or more genes selected from the group consisting of PCNA, CCNA2, and CDK4.

[5-10] The pharmaceutical composition of any one of [7] to [12] and [4-1] to [4-9], which is for increasing the expression of a gene involved in cell cycle suppression in an individual as compared to administration of the bispecific antibody of any one of [7] (a) to (c) or said another anticancer agent alone.

[5-11] The pharmaceutical composition of [5-10], wherein the gene involved in cell cycle suppression is p21.

[5-12] The pharmaceutical composition of any one of [7] to [12] and [4-1] to [4-9], which is for increasing a leukocyte marker in an individual as compared to administration of the bispecific antibody of any one of [7] (a) to (c) or said another anticancer agent alone.

[5-13] The pharmaceutical composition of [5-12], wherein the leukocyte marker is CD45.

[5-14] The pharmaceutical composition of any one of [7] to [12] and [4-1] to [4-9], which is for increasing a T cell marker and/or T cell activation marker in an individual as compared to administration of the bispecific antibody of any one of [7] (a) to (c) or said another anticancer agent alone.

[5-15] The pharmaceutical composition of [5-14], wherein the T cell marker and/or T cell activation marker is one or more T cell markers and/or T cell activation markers selected from the group consisting of CD3, CD4, CD8a, GZB, PRF1, and IFNγ.

[5-16] The pharmaceutical composition of any one of [7] to [12] and [4-1] to [4-9], which is for increasing the expression of an immune checkpoint gene in an individual as compared to administration of the bispecific antibody of any one of [7] (a) to (c) or said another anticancer agent alone.

[5-17] The pharmaceutical composition of [5-16], wherein the immune checkpoint gene is one or more immune checkpoint genes selected from the group consisting of PD-L1, PD-1, TIM3, LAG3, and CTLA4.

In each item of [4-1] to [4-36] above, “another anticancer agent” refers to an anticancer agent which comprises as an active ingredient a substance that is different from the bispecific antibody recited in each item. Specifically, the term “another anticancer agent” merely indicates that the ~~invention~~disclosure of each item is specified as ~~invention~~disclosures in which the other/another anticancer agent is an anticancer agent comprising as an active ingredient a substance that is different from the bispecific antibody, and the ~~invention~~disclosure is not limited to ~~invention~~disclosures in which the bispecific antibody is used as an anticancer agent. For example, even when each ~~invention~~disclosure of

[4-1] to [4-36] recites the term “another anticancer agent”, the ~~invention~~disclosure also includes ~~embodiment~~examples where no other anticancer agent than the “another anticancer agent” is used, and in this case, the ~~invention~~disclosure includes ~~embodiment~~examples where the bispecific antibody is used as an enhancer, combination drug, excipient, or such for the other anticancer agent.

[Effects of the ~~Invention~~Disclosure]

The present ~~invention~~disclosure provides novel multispecific antigen-binding molecules with molecular forms that can be produced with high efficiency, which maintain the strong antitumor activity possessed by BiTE and the excellent safety property of not causing cancer antigen-independent induction of a cytokine storm and such, and have long half-lives in blood. Anticancer agents which comprise a multispecific antigen-binding molecule of the present ~~invention~~disclosure as an active ingredient and combination therapies using the multispecific antigen-binding molecule and another anticancer agent target cancer tissues containing glypican 3-expressing cancer cells to cause cytotoxicity, and can treat or prevent various cancers. The ~~invention~~disclosure enables desirable treatment which has not only a high level of safety but also reduced physical burden, and is highly convenient for patients.

Brief Description of the Drawings

Fig. 1-1 is graphs showing the cytotoxic activity of antibody-38 when cell lines derived from various cancer types are used as target cells.

Fig. 1-2 is graphs showing the cytotoxic activity of antibody-38 when cell lines derived from various cancer types are used as target cells (a continuation of Fig. 1-1).

Fig. 1-3 is graphs showing the cytotoxic activity of antibody-38 when cell lines derived from various cancer types are used as target cells (a continuation of Fig. 1-2).

Fig. 2 is graphs showing the anti-tumor activity of antibody-38 against xenograft tumors derived from various cancer types in a human T cell transplantation model.

Fig. 3 is a graph showing the anti-tumor activities of antibody-39 and -40 against PC-10 xenograft tumor in a human T cell transplantation model.

Fig. 4 is a graph showing the anti-tumor activities of antibody-30, -31, -32, and -33 against SK-HEP-1/hGPC3 (SK-pca31a) xenograft tumor in a human T cell transplantation model.

Fig. 5 is a graph showing the anti-tumor activity of antibody-38 against PC-10 xenograft tumor in a humanized NOG mouse model.

Fig. 6 is a graph showing the anti-tumor activities of antibody-38, and anti-human GPC3 antibody, anti-mouse CTLA-4 antibody, anti-mouse PD-1 antibody, or anti-mouse PD-L1 antibody against LLC1/hGPC3 syngeneic tumor in a human CD3εδγ gene-modified mouse

CLAIMS

~~1. An anticancer agent comprising as an active ingredient a bispecific antibody of any one of (a) to (c) below that comprises an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity:~~

~~(a) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in the antibody variable region having glypican 3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in the antibody variable region having CD3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 168, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;~~

~~(b) a bispecific antibody in which the antibody variable region having glypican 3-binding activity is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 206; the antibody variable region having CD3-binding activity is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 168; and an antibody variable region of a common L chain is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 223; and~~

~~(c) a bispecific antibody which has an antibody H chain having glypican 3-binding activity and having at least 80% identity to the amino acid sequence of SEQ ID NO: 385; an antibody H chain having CD3-binding activity and having at least 80% identity to the amino acid sequence of SEQ ID NO: 402; and common L chains having at least 80% identity to the amino acid sequence of SEQ ID NO: 410.~~

~~2. An anticancer agent comprising as an active ingredient a bispecific antibody that comprises the antibody H chain of SEQ ID NO: 385 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 402 having CD3-binding activity, and the common L chains of SEQ ID NO: 410.~~

~~3. The anticancer agent of claim 1 or 2, wherein the cancer is a glypican 3-positive cancer.~~

~~4. The anticancer agent of claim 3, wherein the glypican 3-positive cancer is a cancer in which the number of glypican 3 antigens on cell surface per cell is 100 or more.~~

~~5. The anticancer agent of any one of claims 1 to 4, wherein the cancer is any cancer selected from the group consisting of gastric cancer, head and neck cancer, esophageal cancer, lung cancer, liver cancer, ovary cancer, breast cancer, colon cancer, kidney cancer, skin cancer, muscle tumor, pancreas cancer, prostate cancer, testis cancer, uterine cancer, cholangiocarcinoma, Merkel cell carcinoma, bladder cancer, thyroid cancer, schwannoma, adrenal cancer, anus cancer, central nervous system tumor, neuroendocrine tissue tumor, penis cancer, pleura tumor, salivary gland tumor, vulva cancer, thymoma, and childhood cancer.~~

~~6. The anticancer agent of any one of claims 1 to 5, which is for treating a patient having cancer that is refractory to treatment with an immune checkpoint inhibitor.~~

~~7~~1. Use of ~~A~~ a pharmaceutical composition in the manufacture of a medicament for treating a glypican 3-positive cancer or for preventing a glypican 3-positve cancer, wherein the pharmaceutical composition is to be used ~~for use~~ in combination with an immune checkpoint inhibitor or an angiogenic inhibitor, ~~another anticancer agent,~~ wherein the pharmaceutical composition comprising as an active ingredient a bispecific antibody of any one of ~~(a) to (c)~~the bispecific antibodies below that comprise~~s~~ an antibody variable region having glypican 3-binding activity and an antibody variable region having CD3-binding activity:

~~(a) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in the antibody variable region having glypican 3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in the antibody variable region having CD3-binding activity are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 168, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are sequences having at least 80% identity to the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;~~

~~(b) a bispecific antibody in which the antibody variable region having glypican 3-binding activity is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 206; the antibody variable region having CD3-binding activity is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 168; and an antibody variable region of a common L chain is a sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 223; and~~

~~(c) a bispecific antibody which has an antibody H chain having glypican 3-binding activity and having at least 80% identity to the amino acid sequence of SEQ ID NO: 385; an antibody H chain having CD3-binding activity and having at least 80% identity to the amino acid sequence~~

~~of SEQ ID NO: 402; and common L chains having at least 80% identity to the amino acid sequence of SEQ ID NO: 410.~~

(1) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 211, respectively; CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 142, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;

(2) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 211, respectively; CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 144, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;

(3) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 144, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;

(4) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 142, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively; and

(5) a bispecific antibody in which CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having glypican 3-binding activity are the amino acid sequences of the CDR1,

CDR2, and CDR3 regions comprised in SEQ ID NO: 206, respectively; CDR1, CDR2, and CDR3 comprised in an antibody H chain variable region having CD3-binding activity are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 168, respectively; and CDR1, CDR2, and CDR3 comprised in an antibody variable region of a common L chain are the amino acid sequences of the CDR1, CDR2, and CDR3 regions comprised in SEQ ID NO: 223, respectively;
wherein the immune checkpoint inhibitor is an anti-CTLA-4 antibody, Pembrolizumab, Nivolumab, MEDI0680, PDR001, BGB-A317, REGN2810, SHR-1210, PF-06801591, Atezolizumab, Avelumab, Durvalumab, MDX-1105, Ipilimumab, Tremelimumab, MBG452, BMS-986016 or LAG525, and wherein the angiogenic inhibitor is Bevacizumab, Sorafenib, Everolimus or Temsirolimus.

2. Use of a pharmaceutical composition in the manufacture of a medicament for treating a glypican 3-positive cancer or for preventing a glypican 3-positive cancer, wherein the pharmaceutical composition is to be used in combination with an immune checkpoint inhibitor or an angiogenic inhibitor, wherein the pharmaceutical composition comprises as an active ingredient a bispecific antibody of any one of the bispecific antibodies below:
(1) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 211; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 142; and a variable region of a common L chain is the amino acid sequence of SEQ ID NO: 223;
(2) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 211; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 144; and a variable region of a common L chain is the amino acid sequence of SEQ ID NO: 223;
(3) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 206; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 144; and a variable region of a common L chain is the amino acid sequence of SEQ ID NO: 223;
(4) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 206; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 142; and a variable region of a common L chain is the amino acid sequence of SEQ ID NO: 223; and
(5) a bispecific antibody in which an antibody H chain variable region having glypican 3-binding activity is the amino acid sequence of SEQ ID NO: 206; an antibody H chain variable region having CD3-binding activity is the amino acid sequence of SEQ ID NO: 168; and a

variable region of a common L chain is the amino acid sequence of SEQ ID NO: 223; wherein the immune checkpoint inhibitor is an anti-CTLA-4 antibody, Pembrolizumab, Nivolumab, MEDI0680, PDR001, BGB-A317, REGN2810, SHR-1210, PF-06801591, Atezolizumab, Avelumab, Durvalumab, MDX-1105, Ipilimumab, Tremelimumab, MBG452, BMS-986016 or LAG525, and wherein the angiogenic inhibitor is Bevacizumab, Sorafenib, Everolimus or Temsirolimus.

3. Use of a pharmaceutical composition in the manufacture of a medicament for treating a glypican 3-positive cancer or for preventing a glypican 3-positive cancer, wherein the pharmaceutical composition is to be used in combination with an immune checkpoint inhibitor or an angiogenic inhibitor, wherein the pharmaceutical composition comprises as an active ingredient a bispecific antibody of any one of the bispecific antibodies below:

(1) a bispecific antibody that has the antibody H chain of SEQ ID NO: 386 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 398 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410;

(2) a bispecific antibody that has the antibody H chain of SEQ ID NO: 386 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 399 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410;

(3) a bispecific antibody that has the antibody H chain of SEQ ID NO: 385 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 399 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410;

(4) a bispecific antibody that has the antibody H chain of SEQ ID NO: 385 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 398 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410; and

(5) a bispecific antibody that has the antibody H chain of SEQ ID NO: 385 having glypican 3-binding activity, the antibody H chain of SEQ ID NO: 402 having CD3-binding activity, and the antibody common L chains of SEQ ID NO: 410;

wherein the immune checkpoint inhibitor is an anti-CTLA-4 antibody, Pembrolizumab, Nivolumab, MEDI0680, PDR001, BGB-A317, REGN2810, SHR-1210, PF-06801591, Atezolizumab, Avelumab, Durvalumab, MDX-1105, Ipilimumab, Tremelimumab, MBG452, BMS-986016 or LAG525, and wherein the angiogenic inhibitor is Bevacizumab, Sorafenib, Everolimus or Temsirolimus.

~~8~~4. The use ~~pharmaceutical composition~~ of any one of claims 1 to 3~~7~~, wherein the bispecific antibody is to be administered simultaneously with said ~~another anticancer agent~~immune checkpoint inhibitor or angiogenic inhibitor.

~~9~~5. ___The use ~~pharmaceutical composition~~ of any one of claims 1 to ~~3~~7, wherein the bispecific antibody is to be administered before or after administration of said immune checkpoint inhibitor or angiogenic inhibitor ~~another anticancer agent~~.

~~10. ___The pharmaceutical composition of any one of claims 7 to 9, wherein said another anticancer agent is a chemotherapeutic agent, a T cell-activating agonist agent, an immune checkpoint inhibitor, or an angiogenic inhibitor.~~

~~11. The pharmaceutical composition of claim 10, wherein the chemotherapeutic agent is an antimetabolite, a plant alkaloid, or a platinum compound.~~

~~12. The pharmaceutical composition of claim 10, wherein the T cell-activating agonist agent is an agonist antibody against TNFRSF.~~

~~13. The pharmaceutical composition of claim 10, wherein the immune checkpoint inhibitor is a PD1 antibody, a PDL1 antibody, a TIM3 antibody, or an LAG3 antibody.~~

~~14. The pharmaceutical composition of claim 10, wherein the angiogenic inhibitor is a VEGFR2 antibody.~~

~~15. An agent for inducing cytotoxicity, an agent for suppressing cell proliferation, an agent for inhibiting cell proliferation, an agent for activating immune response, an agent for treating cancer, or an agent for preventing cancer, which comprises the pharmaceutical composition of any one of claims 7 to 14.~~