TAAs selected from BCMA, CD38 and GPRC5D and CD28 expressed on T-cells have the potency to treat multiple myeloma as single agent or in combination with other agents such as T cell bispecific antibodies (TCBs) targeting a human MM cell surface antigen.

SUMMARY

The present disclosure describes tumor-targeted bispecific agonistic CD28 antigen binding molecules which achieve a tumor-dependent T cell activation and tumor cell killing without the necessity to form multimers. The bispecific CD28 antigen binding molecules of the present disclosure are characterized by monovalent binding to CD28 and in that they comprise at least one antigen binding domain capable of specific binding to a tumor-associated antigen (such as Fibroblast Activation Protein (FAP) or Carcinoembryonic Antigen (CEA), CD19 or GPRC5D). Furthermore, they possess an Fc domain composed of a first and a second subunit capable of stable association comprising one or more amino acid substitution that reduces the binding affinity of the antigen binding molecule to an Fc receptor and/or effector function. Fc receptor-mediated cross-linking is thereby abrogated and tumor-specific activation is achieved by cross-linking through binding of the at least one antigen binding domain capable of specific binding to a tumor-associated antigen to its antigen.

Thus, ~~in one aspect,~~ the disclosure provides a bispecific agonistic CD28 antigen binding molecule characterized by monovalent binding to CD28, comprising
(a) one antigen binding domain capable of specific binding to CD28,
(b) at least one antigen binding domain capable of specific binding to a tumor-associated antigen, and
(c) an Fc domain composed of a first and a second subunit capable of stable association comprising one or more amino acid substitution that reduces the binding affinity of the antigen binding molecule to an Fc receptor and/or effector function.

In one aspect, the present disclosure provides a bispecific agonistic CD28 antigen binding molecule characterized by monovalent binding to CD28, comprising
(a) one Fab fragment capable of specific binding to CD28 comprising
(i) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:47 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:54, or

(ii) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:46 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:53, or

(iii) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:42 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:27,

(b) one crossFab fragment capable of specific binding to CD19 comprising

(i) a heavy chain variable region (V_HCD19) comprising the amino acid sequence of SEQ ID NO:412 and a light chain variable region (V_LCD19) comprising the amino acid sequence of SEQ ID NO:413, or

(ii) a heavy chain variable region (V_HCD19) comprising the amino acid sequence of SEQ ID NO:420 and a light chain variable region (V_LCD19) comprising the amino acid sequence of SEQ ID NO:421, and

(c) a Fc domain of human IgG1 subclass and comprises the amino acid mutations L234A, L235A and P329G, numbered according to Kabat EU index.

In one example, a bispecific agonistic CD28 antigen binding molecule as defined below is provided, wherein the Fc domain is an IgG, particularly an IgG1 Fc domain or an IgG4 Fc domain. In one particular example, the Fc domain composed of a first and a second subunit capable of stable association is an IgG1 Fc domain. In one example, the Fc domain comprises the amino acid substitutions L234A and L235A (numbering according to Kabat EU index). In one example, the Fc domain is of human IgG1 subclass and comprises the amino acid mutations L234A, L235A and P329G (numbering according to Kabat EU index).

In one example, provided is a bispecific agonistic CD28 antigen binding molecule as defined herein before, wherein the antigen binding domain capable of specific binding to CD28 comprises

of producing a bispecific agonistic CD28 antigen binding molecule as described herein comprising culturing the host cell of the disclosure under conditions suitable for the expression of the bispecific agonistic CD28 antigen binding molecule. Optionally, the method also comprises recovering the bispecific agonistic CD28 antigen binding molecule. In another aspect, provided is a method of producing a bispecific agonistic CD28 antigen binding molecule, comprising the steps of a) culturing the host cell of the disclosure under conditions suitable for the expression of the bispecific agonistic CD28 antigen binding molecule and b) optionally recovering the bispecific agonistic CD28 antigen binding molecule. ~~In another aspect, the~~The disclosure also encompasses a bispecific agonistic CD28 antigen binding molecule produced by the method of the disclosure.

In another aspect, the disclosure further provides a pharmaceutical composition comprising a bispecific agonistic CD28 antigen binding molecule of the disclosure and at least one pharmaceutically

acceptable excipient. The pharmaceutical composition is for use in the treatment of cancer. In another aspect, the disclosure provides the pharmaceutical composition of the disclosure for use in the treatment of cancer.

Also encompassed by the disclosure are methods of using the bispecific agonistic CD28 antigen binding molecule and the pharmaceutical composition of the disclosure. In one aspect the disclosure provides a bispecific agonistic CD28 antigen binding molecule or a pharmaceutical composition according to the disclosure for use as a medicament. ~~In one aspect, provided~~Provided is a bispecific agonistic CD28 antigen binding molecule as described herein for use in enhancing (a) cell activation or (b) T cell effector functions. Provided is a bispecific agonistic CD28 antigen binding molecule or a pharmaceutical composition according to the disclosure for use in the treatment of a disease. In a specific example, the disease is cancer. In another aspect, provided is the bispecific agonistic CD28 antigen binding molecule of the disclosure for use in the treatment of cancer. In another aspect, provided is the bispecific agonistic CD28 antigen binding molecule of the disclosure for use in treating a B-cell proliferative disorder selected from the group consisting of Non-Hodgkin lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle-cell lymphoma (MCL), marginal zone lymphoma (MZL), Multiple myeloma (MM) and Hodgkin lymphoma (HL). Provided is a bispecific agonistic CD28 antigen binding molecule or pharmaceutical composition according to the disclosure is for use in the treatment of cancer, wherein the bispecific agonistic CD28 antigen binding molecule is administered in combination with a chemotherapeutic agent, radiation therapy and/ or other agents for use in cancer immunotherapy. In another aspect, provided is the bispecific agonistic CD28 antigen binding molecule of the disclosure for use in the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with a chemotherapeutic agent, radiation therapy and/ or other agents for use in cancer immunotherapy. Provided is a bispecific agonistic CD28 antigen binding molecule or a pharmaceutical composition for use in the treatment of cancer, wherein the bispecific agonistic CD28 antigen binding molecule is administered in combination with a T-cell activating anti-CD3 bispecific antibody. In another aspect, provided is the bispecific agonistic CD28 antigen binding molecule of the disclosure for use in the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with a T-cell activating anti-CD3 bispecific antibody. In another aspect, provided is the bispecific agonistic CD28 antigen binding molecule of the disclosure for use in the treatment of cancer, wherein the agonistic CD28 antigen

binding molecule is to be administered in combination with an anti-CD20/anti-CD3 bispecific antibody. In another aspect, provided is the bispecific agonistic CD28 antigen binding molecule of the disclosure for use in the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-CD20/anti-CD3 bispecific antibody comprising a polypeptide sequence of SEQ ID NO: 455, a polypeptide sequence of SEQ ID NO: 456, a polypeptide sequence of SEQ ID NO: 457 and a polypeptide sequence of SEQ ID NO: 458. Provided is a bispecific agonistic CD28 antigen binding molecule or a pharmaceutical composition for use in the treatment of cancer, wherein the bispecific agonistic CD28 antigen binding molecule is administered in combination with an anti-PD-L1 antibody or an anti-PD-1 antibody. In another aspect, provided is the bispecific agonistic CD28 antigen binding molecule of the disclosure for use in the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-PD-L1 antibody or an anti-PD-1 antibody.

Also provided is the use of a bispecific agonistic CD28 antigen binding molecule according to the disclosure in the manufacture of a medicament for the treatment of a disease; as well as a method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a bispecific agonistic CD28 antigen binding molecule according to the disclosure or a composition comprising the bispecific agonistic CD28 antigen binding molecule according to the disclosure in a pharmaceutically acceptable form. In a specific example, the disease is cancer. In another aspect, provided is the use of the bispecific agonistic CD28 antigen binding molecule of the disclosure, or the pharmaceutical composition of the disclosure, in the manufacture of a medicament for the treatment of cancer. In another aspect, provided is use of of the bispecific agonistic CD28 antigen binding molecule of the disclosure in the manufacture of a medicament for treating a B-cell proliferative disorder selected from the group consisting of Non-Hodgkin lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle-cell lymphoma (MCL), marginal zone lymphoma (MZL), Multiple myeloma (MM) and Hodgkin lymphoma (HL). In another aspect, provided is the use of the bispecific agonistic CD28 antigen binding molecule of the disclosure in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with a chemotherapeutic agent, radiation therapy and/ or other agents for use in cancer immunotherapy. In another aspect, provided is the use of the bispecific agonistic CD28 antigen binding molecule of the disclosure in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be

administered in combination with a T-cell activating anti-CD3 bispecific antibody. In another aspect, provided is use of the bispecific agonistic CD28 antigen binding molecule of the disclosure in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-CD20/anti-CD3 bispecific antibody. In another aspect, provided is use of the bispecific agonistic CD28 antigen binding molecule of the disclosure in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-CD20/anti-CD3 bispecific antibody comprising a polypeptide sequence of SEQ ID NO: 455, a polypeptide sequence of SEQ ID NO: 456, a polypeptide sequence of SEQ ID NO: 457 and a polypeptide sequence of SEQ ID NO: 458. In another aspect, provided is the use of the bispecific agonistic CD28 antigen binding molecule of the disclosure in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-PD-L1 antibody or an anti-PD-1 antibody. Provided is a method (a) enhancing cell activation or (b) enhancing T cell effector functions in an individual, comprising administering a bispecific agonistic CD28 antigen binding molecule according to the disclosure or a composition comprising the bispecific agonistic CD28 antigen binding molecule according to the disclosure in a pharmaceutically acceptable form to said individual. Provided is the use of a bispecific agonistic CD28 antigen binding molecule according to the disclosure in the manufacture of a medicament for the treatment of a disease, wherein the treatment comprises co-administration with a chemotherapeutic agent, radiation therapy and/ or other agents for use in cancer immunotherapy. Provided is a method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a

Claims

1. A bispecific agonistic CD28 antigen binding molecule characterized by monovalent binding to CD28, comprising

(a) one ~~antigen binding domain~~Fab fragment capable of specific binding to CD28 comprising

(i) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:47 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:54, or

(ii) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:46 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:53, or

(iii) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:42 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:27,

(b) ~~at least~~ one ~~antigen binding domain~~crossFab fragment capable of specific binding to ~~a tumor-associated antigen~~CD19 comprising

(i) a heavy chain variable region (V_HCD19) comprising the amino acid sequence of SEQ ID NO:412 and a light chain variable region (V_LCD19) comprising the amino acid sequence of SEQ ID NO:413, or

(ii) a heavy chain variable region (V_HCD19) comprising the amino acid sequence of SEQ ID NO:420 and a light chain variable region (V_LCD19) comprising the amino acid sequence of SEQ ID NO:421, and

(c) a Fc domain of human IgG1 subclass and comprises the amino acid mutations L234A, L235A and P329G, numbered according to Kabat EU index~~composed of a first and a second subunit capable of stable association comprising one or more amino acid substitution that reduces the binding affinity of the antigen binding molecule to an Fc receptor and/or effector function~~.

2. The bispecific agonistic CD28 antigen binding molecule of claim 1, wherein the Fab fragment capable of specific binding to CD28 comprises a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:47 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:54.

3. The bispecific agonistic CD28 antigen binding molecule of claim 1, wherein the Fab fragment capable of specific binding to CD28 comprises a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:46 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:53.

2. The bispecific agonistic CD28 antigen binding molecule of claim 1, wherein the Fc domain is of human IgG1 subclass and comprises the amino acid mutations L234A, L235A and P329G (numbering according to Kabat EU index).

3. The bispecific agonistic CD28 antigen binding molecule of claims 1 or 2, wherein the antigen binding domain capable of specific binding to CD28 comprises
(i) a heavy chain variable region (V_HCD28) comprising a heavy chain complementary determining region CDR-H1 of SEQ ID NO: 36, a CDR-H2 of SEQ ID NO: 37, and a CDR-H3 of SEQ ID NO: 38, and a light chain variable region (V_LCD28) comprising a light chain complementary determining region CDR-L1 of SEQ ID NO: 39, a CDR-L2 of SEQ ID NO: 40 and a CDR-L3 of SEQ ID NO: 41; or
(ii) a heavy chain variable region (V_HCD28) comprising a CDR-H1 of SEQ ID NO: 20, a CDR-H2 of SEQ ID NO: 21, and a CDR-H3 of SEQ ID NO: 22, and a light chain variable region (V_LCD28) comprising a CDR-L1 of SEQ ID NO: 23, a CDR-L2 of SEQ ID NO: 24 and a CDR-L3 of SEQ ID NO: 25.

4. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 3, wherein the antigen binding domain capable of specific binding to CD28 comprises a heavy chain variable region (V_HCD28) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:26, and a light chain variable region (V_LCD28) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:27.

5. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 4, wherein the antigen binding domain capable of specific binding to CD28 comprises a heavy chain variable region (V_HCD28) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50 and SEQ ID NO:51, and a light chain variable region (V_LCD28) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:27, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60 and SEQ ID NO:61.

6. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 3 or 5, wherein the antigen binding domain capable of specific binding to CD28 comprises
(a) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:47 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:54, or

~~(b) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:47 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:27, or~~

~~(c) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:51 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:61, or~~

~~(d) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:46 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:53, or~~

~~(e) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:46 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:54, or~~

~~(f) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:46 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:59, or~~

~~(g) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:46 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:27, or~~

~~(h) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:43 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:27, or~~

~~(i) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:42 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:53, or~~

~~(j) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:42 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:59, or~~

~~(k) a heavy chain variable region (V_HCD28) comprising the amino acid sequence of SEQ ID NO:42 and a light chain variable region (V_LCD28) comprising the amino acid sequence of SEQ ID NO:27.~~

~~7. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 6, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is selected from the group consisting of Fibroblast Activation Protein (FAP), Carcinoembryonic Antigen (CEA), Folate receptor alpha (FolR1), Melanoma-associated Chondroitin Sulfate Proteoglycan (MCSP), Epidermal Growth Factor Receptor (EGFR), human epidermal growth factor receptor 2 (HER2), p95HER2, epithelial cell adhesion molecule (EpCAM), HER3, CD30, TPBG (5T4), CD19, CD79b, CD20, CD22, CD37, CD38, BCMA and GPRC5D.~~

~~8. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to Carcinoembryonic Antigen (CEA).~~

~~9. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 8, wherein the antigen binding domain capable of specific binding to CEA comprises~~
~~(i) a heavy chain variable region (V_HCEA) comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:188, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:189, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:190, and a light chain variable region (V_LCEA) comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:191, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:192, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:193; or~~
~~(ii) a heavy chain variable region (V_HCEA) comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:180, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:181, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:182, and a light chain variable region (V_LCEA) comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:183, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:184, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:185; or~~
~~(iii) a heavy chain variable region (V_HCEA) comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:127, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:128, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:129, and a light chain variable region (V_LCEA) comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:130, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:131, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:132,~~
~~(iv) a heavy chain variable region (V_HCEA) comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:507, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:508, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:509, and a light chain variable region (V_LCEA) comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:510, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:511, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:512.~~

~~10. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 9, wherein the antigen binding domain capable of specific binding to CEA comprises a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:186, and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:187.~~

~~11. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 9, wherein the antigen binding domain capable of specific binding to CEA comprises~~

~~(a) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:194 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:195, or~~

~~(b) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:196 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:197, or~~

~~(c) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:198 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:199, or~~

~~(d) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:200 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:201, or~~

~~(e) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:202 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:203, or~~

~~(f) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:204 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:205, or~~

~~(g) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:206 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:207, or~~

~~(h) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:208 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:209, or~~

~~(i) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:210 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:211, or~~

~~(j) a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:212 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:213.~~

~~12. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 9 or 11, wherein the antigen binding domain capable of specific binding to CEA comprises a heavy chain variable region (V_HCEA) comprising the amino acid sequence of SEQ ID NO:200 and a light chain variable region (V_LCEA) comprising the amino acid sequence of SEQ ID NO:201.~~

~~13. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to Fibroblast Activation Protein (FAP).~~

~~14. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 13, wherein the antigen binding domain capable of specific binding to FAP comprises~~

~~(a) a heavy chain variable region (V_HFAP) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:12, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:13, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, and a light chain variable region (V_LFAP) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:15, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:16, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:17, or~~

~~(b) a heavy chain variable region (V_HFAP) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:4, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:6, and a light chain variable region (V_LFAP) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:7, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:8, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:9.~~

~~15. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 13 or 14, wherein the antigen binding domain capable of specific binding to FAP comprises a heavy chain variable region (V_HFAP) comprising the amino acid sequence of SEQ ID NO:18 and a light chain variable region (V_LFAP) comprising the amino acid sequence of SEQ ID NO:19.~~

~~16. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to epithelial cell adhesion molecule (EpCAM).~~

~~17. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 16, wherein the antigen binding domain capable of specific binding to EpCAM comprises comprises a heavy chain variable region (V_HEpCAM) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:515, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:516, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:517, and a light chain variable region (V_LEpCAM) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:518, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:519, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:520.~~

~~18. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 16 or 17, wherein the antigen binding domain capable of specific binding to EpCAM comprises a heavy chain variable region (V_HEpCAM) comprising the amino acid sequence of SEQ ID~~

~~NO:521 and a light chain variable region (V_LEpCAM) comprising the amino acid sequence of SEQ ID NO:522.~~

~~19. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to HER3.~~

~~20. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 19, wherein the antigen binding domain capable of specific binding to HER3 comprises a heavy chain variable region (V_HHER3) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:523, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:524, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:525, and a light chain variable region (V_LHER3) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:526, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:527, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:528.~~

~~21. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 19 or 20, wherein the antigen binding domain capable of specific binding to HER3 comprises a heavy chain variable region (V_HHER3) comprising the amino acid sequence of SEQ ID NO:529 and a light chain variable region (V_LHER3) comprising the amino acid sequence of SEQ ID NO:530.~~

~~22. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to CD30.~~

~~23. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 22, wherein the antigen binding domain capable of specific binding to CD30 comprises a heavy chain variable region (V_HCD30) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:531, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:532, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:533, and a light chain variable region (V_LCD30) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:534, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:535, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:536.~~

~~24. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 22 or 23, wherein the antigen binding domain capable of specific binding to CD30 comprises a heavy chain variable region (V_HCD30) comprising the amino acid sequence of SEQ ID NO:537 and a light chain variable region (V_LCD30) comprising the amino acid sequence of SEQ ID NO:538.~~

~~25. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to TBPG.~~

~~26. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 25, wherein the antigen binding domain capable of specific binding to TBPG comprises a heavy chain variable region (V_HTBPG) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:539, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:540, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:541, and a light chain variable region (V_LTBPG) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:542, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:543, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:544.~~

~~27. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 25 or 26, wherein the antigen binding domain capable of specific binding to TBPG comprises a heavy chain variable region (V_HTBPG) comprising the amino acid sequence of SEQ ID NO:545 and a light chain variable region (V_LTBPG) comprising the amino acid sequence of SEQ ID NO:546.~~

~~28. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is a Multiple Myeloma (MM) cell surface antigen selected from the group consisting of CD38, BCMA and GPRC5D.~~

~~29. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 28, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to GPRC5D.~~

~~30. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 28 or 29, wherein the antigen binding domain capable of specific binding to GPRC5D comprises (a) a heavy chain variable region (V_HGPRC5D) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:563, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:564, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:565, and a light chain variable region (V_LGPRC5D) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:566, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:567, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:568, or (b) a heavy chain variable region (V_HGPRC5D) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:579, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:580, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:581, and a light chain variable region (V_LGPRC5D) comprising (iv) CDR-L1 comprising the amino acid~~

sequence of SEQ ID NO:582, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:583, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:584.

31. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 28 to 30, wherein the antigen binding domain capable of specific binding to GPRC5D comprises a heavy chain variable region (V_HGPRC5D) comprising the amino acid sequence of SEQ ID NO:569 and a light chain variable region (V_LGPRC5D) comprising the amino acid sequence of SEQ ID NO:570.

32. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 28, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to CD38.

33. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 28 or 32, wherein the antigen binding domain capable of specific binding to CD38 comprises a heavy chain variable region (V_HCD38) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:547, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:548, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:549, and a light chain variable region (V_LCD38) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:550, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:551, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:552.

34. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 28 or 32 or 33, wherein the antigen binding domain capable of specific binding to CD38 comprises a heavy chain variable region (V_HCD38) comprising the amino acid sequence of SEQ ID NO:553 and a light chain variable region (V_LCD38) comprising the amino acid sequence of SEQ ID NO:554.

35. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 28, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to BCMA.

36. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 28 or 35, wherein the antigen binding domain capable of specific binding to BCMA comprises a heavy chain variable region (V_HBCMA) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:555, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:556, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:557, and a light chain variable region (V_LBCMA) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:558, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:559, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:560.

~~37. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 28 or 35 or 36, wherein the antigen binding domain capable of specific binding to BCMA comprises a heavy chain variable region (V_HBCMA) comprising the amino acid sequence of SEQ ID NO:561 and a light chain variable region (V_LBCMA) comprising the amino acid sequence of SEQ ID NO:562.~~

~~38. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is a B cell surface antigen selected from the group consisting of CD19, CD79b, CD20, CD22 and CD37.~~

~~39. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 38, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to CD19.~~

~~40. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 38 or 39, wherein the antigen binding domain capable of specific binding to CD19 comprises (a) a heavy chain variable region (V_HCD19) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:406, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:407, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:408, and a light chain variable region (V_LCD19) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:409, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:410, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:411, or (b) a heavy chain variable region (V_HCD19) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:414, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:415, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:416, and a light chain variable region (V_LCD19) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:417, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:418, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:419.~~

~~41. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 38 or 39 or 40, wherein the antigen binding domain capable of specific binding to CD19 comprises (a) a heavy chain variable region (V_HCD19) comprising an amino acid sequence that is at least about 95%, 98% or 100% identical to the amino acid sequence of SEQ ID NO:412, and a light chain variable region (V_LCD19) comprising an amino acid sequence that is at least about 95%, 98% or 100% identical to the amino acid sequence of SEQ ID NO:413, or (b) a heavy chain variable region (V_HCD19) comprising an amino acid sequence that is at least about 95%, 98% or 100% identical to the amino acid sequence of SEQ ID NO:420, and a light chain~~

~~variable region (V_LCD19) comprising an amino acid sequence that is at least about 95%, 98% or 100% identical to the amino acid sequence of SEQ ID NO:421.~~

~~42~~4. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~7 or 38 to 41~~3, wherein the antigen binding domain capable of specific binding to CD19 comprises a heavy chain variable region (V_HCD19) comprising an amino acid sequence of SEQ ID NO:412 and a light chain variable region (V_LCD19) comprising an amino acid sequence of SEQ ID NO:413.

5. The bispecific agonistic CD28 antigen binding molecule of claim 1 comprising a first light chain comprising the amino acid sequence of SEQ ID NO:122, a first heavy chain comprising the amino acid sequence of SEQ ID NO:114, a second heavy chain comprising the amino acid sequence of SEQ ID NO:430 and a second light chain comprising the amino acid sequence of SEQ ID NO:431.

6. The bispecific agonistic CD28 antigen binding molecule of claim 1 comprising the amino acid sequence of SEQ ID NO:121, a first heavy chain comprising the amino acid sequence of SEQ ID NO:116, a second heavy chain comprising the amino acid sequence of SEQ ID NO:430 and a second light chain comprising the amino acid sequence of SEQ ID NO:431.

~~43. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 38, wherein the antigen binding domain capable of specific binding to a tumor-associated antigen is an antigen binding domain capable of specific binding to CD79b.~~

~~44. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 38 or 43, wherein the antigen binding domain capable of specific binding to CD79b comprises a heavy chain variable region (V_HCD79b) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:422, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:423, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:424, and a light chain variable region (V_LCD79b) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:425, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:426, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:427.~~

~~45. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 7 or 38 or 43 or 44, wherein the antigen binding domain capable of binding to CD79b comprises a heavy chain variable region (V_HCD79b) comprising the amino acid sequence of SEQ ID NO:428, and a light chain variable region (V_LCD79b) comprising the amino acid sequence of SEQ ID NO:429.~~

~~46. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 45, comprising~~

~~(a) one Fab fragment capable of specific binding to CD28,~~

~~(b) one crossFab fragment capable of specific binding to a tumor-associated antigen, and~~

~~(c) a Fc domain composed of a first and a second subunit capable of stable association comprising one or more amino acid substitution that reduces the binding affinity of the antigen binding molecule to an Fc receptor and/or effector function.~~

~~47. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 45, comprising~~

~~(a) a first Fab fragment capable of specific binding to CD28,~~

~~(b) a second Fab fragment capable of specific binding to a tumor-associated antigen, and~~

~~(c) a Fc domain composed of a first and a second subunit capable of stable association comprising one or more amino acid substitution that reduces the binding affinity of the antigen binding molecule to an Fc receptor and/or effector function,~~

~~wherein the first Fab fragment capable of specific binding to CD28 is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second Fab fragment capable of specific binding to a tumor-associated antigen, which is in turn fused at its C-terminus to the N-terminus of one of the Fc domain subunits.~~

~~48. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 45, comprising~~

~~(a) a first Fab fragment capable of specific binding to CD28,~~

~~(b) a second and a third Fab fragment capable of specific binding to a tumor-associated antigen, and~~

~~(c) a Fc domain composed of a first and a second subunit capable of stable association comprising one or more amino acid substitution that reduces the binding affinity of the antigen binding molecule to an Fc receptor and/or effector function,~~

~~wherein the first Fab fragment capable of specific binding to CD28 is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second Fab fragment capable of specific binding to a tumor-associated antigen, which is in turn fused at its C-terminus to the N-terminus of the first Fc domain subunit, and the third Fab fragment capable of specific binding to a tumor-associated antigen is fused at the C-terminus of the Fab heavy chain to the N-terminus of the second Fc domain subunit.~~

~~49~~7. One or more isolated polynucleotide encoding the bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~6.

~~50~~8. One or more vector, particularly expression vector, comprising the polynucleotide(s) of claim ~~49~~7.

~~51~~9. A host cell comprising the polynucleotide(s) of claim ~~49 -~~7 or the vector(s) of claim ~~50~~8.

~~52~~10. A method of producing a bispecific agonistic CD28 antigen binding molecule, comprising the steps of a) culturing the host cell of claim ~~51 -~~9 under conditions suitable for the expression of the bispecific agonistic CD28 antigen binding molecule and b) optionally recovering the bispecific agonistic CD28 antigen binding molecule.

~~53. A bispecific agonistic CD28 antigen binding molecule, produced by the method of claim 52.~~

~~54~~11. A pharmaceutical composition comprising the bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48 -~~6 and at least one pharmaceutically acceptable excipient.

~~55~~12. The pharmaceutical composition of claim ~~54 -~~11 for use in the treatment of cancer.

~~56~~13. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~6, or the pharmaceutical composition of claim ~~54~~11, for use as a medicament.

~~57. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 48 for use in enhancing (a) T cell activation or (b) T cell effector functions.~~

~~58~~14. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~ 6 for use in the treatment of cancer.

15. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 6 for use in treating a B-cell proliferative disorder selected from the group consisting of Non-Hodgkin lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle-cell lymphoma (MCL), marginal zone lymphoma (MZL), Multiple myeloma (MM) and Hodgkin lymphoma (HL).

~~59~~16. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~ 6 for use in the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with a chemotherapeutic agent, radiation therapy and/ or other agents for use in cancer immunotherapy.

~~60~~17. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~ 6 for use in the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with a T-cell activating anti-CD3 bispecific antibody.

18. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 6 for use in the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-CD20/anti-CD3 bispecific antibody.

19. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 6 for use in the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-CD20/anti-CD3 bispecific antibody comprising a polypeptide sequence of SEQ ID NO: 455, a polypeptide sequence of SEQ ID NO: 456, a polypeptide sequence of SEQ ID NO: 457 and a polypeptide sequence of SEQ ID NO: 458.

~~61~~20. The bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~ 6 for use in the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-PD-L1 antibody or an anti-PD-1 antibody.

~~62~~21. Use of the bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~6, or the pharmaceutical composition of claim ~~54~~11, in the manufacture of a medicament for the treatment of cancer.

22. Use of the bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 6 in the manufacture of a medicament for treating a B-cell proliferative disorder selected from the group consisting of Non-Hodgkin lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle-cell lymphoma (MCL), marginal zone lymphoma (MZL), Multiple myeloma (MM) and Hodgkin lymphoma (HL).

~~63~~23. Use of the bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~ 6 in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with a chemotherapeutic agent, radiation therapy and/ or other agents for use in cancer immunotherapy.

~~64~~24. Use of the bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~ 6 in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with a T-cell activating anti-CD3 bispecific antibody.

25. Use of the bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 6 in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28

antigen binding molecule is to be administered in combination with an anti-CD20/anti-CD3 bispecific antibody.

26. Use of the bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to 6 in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-CD20/anti-CD3 bispecific antibody comprising a polypeptide sequence of SEQ ID NO: 455, a polypeptide sequence of SEQ ID NO: 456, a polypeptide sequence of SEQ ID NO: 457 and a polypeptide sequence of SEQ ID NO: 458.

~~65~~27. Use of the bispecific agonistic CD28 antigen binding molecule of any one of claims 1 to ~~48~~ 6 in the manufacture of a medicament for the treatment of cancer, wherein the agonistic CD28 antigen binding molecule is to be administered in combination with an anti-PD-L1 antibody or an anti-PD-1 antibody.

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