[Patent Literature 4] WO2017/161333

[Patent Literature 5] WO2018/177966

[Patent Literature 6] WO2018/189611

[Patent Literature 7] WO2012/073985

[Patent Literature 8] WO2013/180200

NON PATENT LITERATURE

[0008]

[Non Patent Literature 1] Grupp et al. 2013 N Engl J Med 368(16): 1509- 18

[Non Patent Literature 2] Maude et al. 2014 2014 N Engl J Med 371(16): 1507-17

[Non Patent Literature 3] Kim et al. J Am Chem Soc 2015; 137: 2832-2835

[Non Patent Literature 4] Tamada et al. Clin Cancer Res 2012; 18(23): 6436-6445

[Non Patent Literature 5] Kontermann, mAbs 2012; 4: 182-197.

[Non Patent Literature 6] Mezzanzanica et al., International journal of cancer 1988; 41: 609-615.

[Non Patent Literature 7] Staerz and Bevan, Proceedings of the National Academy of Sciences of the United States of America 1986; 83: 1453-1457.

[Non Patent Literature 8] Staerz et al., Nature 1985; 314: 628-631.

SUMMARY

[0008a] In one aspect, the present disclosure relates to a use of a pharmaceutical composition and a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification, in the manufacture of a medicament for combination therapy to treat cancer, wherein the pharmaceutical composition comprises a cell expressing a chimeric receptor, wherein the cell is a T cell, a natural killer (NK) cell or a macrophage, the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain, the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation, the extracellular binding domain does not specifically bind to an antibody free of the mutation, and the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K.

In another aspect, the present disclosure relates to a use of a pharmaceutical composition in the manufacture of a first medicament and use of a mutated antibody which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification, in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer, wherein the pharmaceutical composition comprises a cell expressing a chimeric receptor, wherein the cell is a T cell, a natural killer (NK) cell or a macrophage, the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain, the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation, the extracellular binding domain does not specifically bind to an antibody free of the mutation, and the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K. In another aspect, the present disclosure relates to a use of a pharmaceutical composition in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein said medicament is to be administered in combination with a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification, wherein the pharmaceutical composition comprises a cell expressing a chimeric receptor, wherein the cell is a T cell, a natural killer (NK) cell or a macrophage, the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain, the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation, the extracellular binding domain does not specifically bind to an antibody free of the mutation, and the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K.

[0008b] In another aspect, the present disclosure relates to a use of a pharmaceutical composition and a cell

expressing a chimeric receptor in the manufacture of a medicament for combination therapy to treat cancer, wherein the cell is a T cell, a natural killer (NK) cell or a macrophage, the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification, the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain, the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation, and the extracellular binding domain does not specifically bind to an antibody free of the mutation, and the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations wherein the mutation is 235R, 236R and 239K . In yet another aspect, the present disclosure provides a use of a pharmaceutical composition in the manufacture of a first medicament and use of a cell expressing a chimeric receptor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer, wherein the cell is a T cell, a natural killer (NK) cell or a macrophage, the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification, the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain, the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation, and the extracellular binding domain does not specifically bind to an antibody free of the mutation, and the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K. In yet another aspect, the present disclosure provides a use of a pharmaceutical composition in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein said medicament

is to be administered in combination with a cell expressing a chimeric receptor, wherein the cell is a T cell, a natural killer (NK) cell or a macrophage, the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification, the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain, the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation, and the extracellular binding domain does not specifically bind to an antibody free of the mutation, and the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K.

[0008c] In another aspect, the present disclosure relates to a use of a pharmaceutical composition and a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, in the manufacture of a medicament for combination therapy to treat cancer, wherein the pharmaceutical composition comprises a bispecific antibody, and the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and the mutation has mutations at position 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K. In yet another aspect, the present disclosure relates to a use of a pharmaceutical composition in the manufacture of a first medicament and use of a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer, wherein the pharmaceutical composition comprises a bispecific antibody, and the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to

the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and, the mutation has mutations at position 235, 236, and 239, each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K.. In yet another aspect, the present disclosure relates to a use of a pharmaceutical composition in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein said medicament is to be administered in combination with a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, wherein the pharmaceutical composition comprises a bispecific antibody, and the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and the mutation has mutations at 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K.

[0008d] In another aspect, the present disclosure relates to a use of a pharmaceutical composition and a bispecific antibody in the manufacture of a medicament for combination therapy to treat cancer, wherein the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, and the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, , and the mutation has mutations at positions 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K. In yet another aspect, the present disclosure relates to a use of a pharmaceutical composition in the manufacture of a first medicament and use of a bispecific antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer, wherein the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, and the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via a moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and the mutation has mutations at 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K. In yet

another aspect, the present disclosure relates to a use of a pharmaceutical composition in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein said medicament is to be administered in combination with a bispecific antibody, wherein the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, and the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and the mutation has mutations at 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K.

[0008e] In yet another aspect, the present disclosure relates to an isolated nucleic acid encoding a chimeric receptor or a bispecific antibody contained in a use as described herein. In yet another aspect, the present disclosure relates to a vector comprising an isolated nucleic acid as described herein. In yet another aspect, the present disclosure relates to a cell transformed or transduced with an isolated nucleic acid as described herein or a vector as described herein.

TECHNICAL PROBLEM

[0009] In spite of therapy using CAR-T cells regarded as promising treatment of cancer patients, there are some limitations on the expansion of the clinical application of the CAR-T cells. First of all, a single tumor antigen is not universally expressed in every cancer. Therefore, the antigen recognition site of CAR needs to be constructed for each targeted tumor antigen. Secondly, economical cost and labor associated with operations for identifying antigen recognition sites for various tumor antigens and newly establishing CAR-T cells harboring these sites are major problems. Thirdly, tumor antigens targeted by CAR may cause tumor immune escape in such a way that treatment decreases their expression levels or mutates the tumor antigens. Particularly, existing CAR-T cells recognize only one target antigen. Therefore, the tumor immune escape causes reduction or disappearance of

CLAIMS

1. Use of a pharmaceutical composition and a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification, in the manufacture of a medicament for combination therapy to treat cancer, wherein

the pharmaceutical composition comprises a cell expressing a chimeric receptor, wherein the cell is a T cell, a natural killer (NK) cell, or macrophage,

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain,

the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation,

the extracellular binding domain does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K.

2. Use of a pharmaceutical composition in the manufacture of a first medicament and use of a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification, in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer,

wherein

the pharmaceutical composition comprises a cell expressing a chimeric receptor, wherein the cell is a T cell, a natural killer (NK) cell, or macrophage,

the chimeric receptor comprises an extracellular binding domain, a transmembrane

domain and an intracellular signaling domain,

the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation,

the extracellular binding domain does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K .

3. Use of a pharmaceutical composition in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein said medicament is to be administered in combination with a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification,

wherein

the pharmaceutical composition comprises a cell expressing a chimeric receptor, wherein the cell is a T cell, a natural killer (NK) cell, or macrophage,

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain,

the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation,

the extracellular binding domain does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K.

4. Use of a pharmaceutical composition and a cell expressing a chimeric receptor in the manufacture of a medicament for combination therapy to treat cancer, wherein

the cell is a T cell, a natural killer (NK) cell, or macrophage,

the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification,

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain,

the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation, and

the extracellular binding domain does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K.

5. Use of a pharmaceutical composition in the manufacture of a first medicament and use of a cell expressing a chimeric receptor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer, wherein

the cell is a T cell, a natural killer (NK) cell, or macrophage,

the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification,

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain,

the mutated antibody is capable of binding to the extracellular binding domain of the

chimeric receptor via the moiety having the mutation, and

the extracellular binding domain does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K.

6. Use of a pharmaceutical composition in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein said medicament is to be administered in combination with a cell expressing a chimeric receptor, wherein

the cell is a T cell, a natural killer (NK) cell, or macrophage,

the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification,

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain,

the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via the moiety having the mutation, and

the extracellular binding domain does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at positions 235, 236, and 239, each represented by its position according to the EU numbering, and the extracellular binding domain binds to the mutated antibody via the moiety having the mutations, wherein the mutation is 235R, 236R and 239K.

7. Use of a pharmaceutical composition and a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution,

deletion, addition or modification of at least one amino acid in a CH2 region, in the manufacture of a medicament for combination therapy to treat cancer, wherein

the pharmaceutical composition comprises a bispecific antibody, and

the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at position 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K.

8. Use of a pharmaceutical composition in the manufacture of a first medicament and use of a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer,

wherein

the pharmaceutical composition comprises a bispecific antibody, and

the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at position 235, 236, and 239, each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K.

9. Use of a pharmaceutical composition in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein said medicament is to be administered in

combination with a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region,

wherein

the pharmaceutical composition comprises a bispecific antibody, and

the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K.

10. Use of a pharmaceutical composition and a bispecific antibody in the manufacture of a medicament for combination therapy to treat cancer, wherein

the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, and

the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at positions 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K.

11. Use of a pharmaceutical composition in the manufacture of a first medicament and use of a bispecific antibody in the manufacture of a second medicament, wherein the first and

second medicaments are to be used in combination therapy to treat cancer,

wherein

the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, and

the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K.

12. Use of a pharmaceutical composition in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein said medicament is to be administered in combination with a bispecific antibody,

wherein

the pharmaceutical composition comprises a mutated antibody, which is capable of binding to a tumor antigen, comprising a moiety having a mutation, including substitution, deletion, addition or modification of at least one amino acid in a CH2 region, and

the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via the moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation, and

the mutation has mutations at 235, 236, and 239 each represented by its position according to the EU numbering, wherein the mutation is 235R, 236R and 239K.

13. An isolated nucleic acid encoding a chimeric receptor according to any one of claims 1 to 12 or the bispecific antibody contained in a use according to any one of claims 7 to 12.

14. A vector comprising the isolated nucleic acid according to claim 13.

15. The vector according to claim 14, wherein the vector is operably linkable to at least one regulatory element for the expression of the chimeric receptor or the bispecific antibody.

16. A cell transformed or transduced with the isolated nucleic acid according to claim 13 or the vector according to claim 14 or 15.