ADCC, which is mediated by the recruitment of NK cells or macrophages as effector cells, as the mechanism for their antitumor effects, a T cell-redirecting antibody is a bispecific antibody comprising an antibody against any one of the subunits constituting the T-cell receptor (TCR) complex on T cells, in particular, an antibody that binds to the CD3 epsilon chain; and an antibody that binds to an antigen on the target cancer cell. T cells come close to cancer cells via simultaneous binding of the T cell-redirecting antibody to the CD3 epsilon chain and a cancer antigen. As a result, antitumor effects against cancer cells are considered to be exerted through the cytotoxic activity possessed by T cells. For example, in recent years, novel T cell-redirecting antibodies have been provided, which are antibodies whose two Fabs respectively bind to a cancer antigen (GPC3) and the CD3ε chain expressed on T cells, and have an Fc region with reduced FcγR-binding activity (PTL 1 and 2).

[0005]

On the other hand, occurrence of toxicity associated with exertion of high antitumor activity by the T cell-redirecting antibody, for example, development of cytokine release syndrome (CRS), has been reported (NPL 8).

[Citation List]

[Patent Literature]

[0006]

[PTL 1] WO2012/073985 (TRAB concept patent)
[PTL 2] WO2016/047722 (ERY974 product patent)

[Non-Patent Literature]

[0007]

[NPL 1] Nat. Biotechnol. (2005) 23, 1073-1078
[NPL 2] Eur J Pharm Biopharm. (2005) 59 (3), 389-396
[NPL 3] Drug Des Devel Ther (2009) 3, 7-16
[NPL 4] Clin Cancer Res. (2010) 16 (1), 11-20
[NPL 5] Nature (1985) 314 (6012), 628-31
[NPL 6] Int J Cancer (1988) 41 (4), 609-15.
[NPL 7] Proc Natl Acad Sci USA (1986) 83 (5), 1453-7
[NPL 8] Cancer J. 2014 Mar-Apr; 20(2): 119-122.

[Summary ~~of Invention~~]

[0007a]

In one aspect, the present disclosure refers to a use of an anti-T cell antigen-binding molecule and a vascular epithelial cell growth factor (VEGF) inhibitor in the manufacture of a

medicament for combination therapy to prevent and/or alleviate and/or treat cytokine release syndrome and/or cytokine release, wherein the anti-T cell antigen-binding molecule comprises (1) a domain comprising an antibody variable region having CD3-binding activity; and (2) a domain comprising an antibody variable region having glypican 3-binding activity, and wherein the VEGF inhibitor is selected from the group consisting of Bevacizumab, Ramucirumab, and Aflibercept.

[0007b]

In another aspect, the present disclosure refers to a use of an anti-T cell antigen-binding molecule in the manufacture of a first medicament and use of a vascular epithelial cell growth factor (VEGF) inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to prevent and/or alleviate and/or treat cytokine release syndrome and/or cytokine release, wherein the anti-T cell antigen-binding molecule comprises (1) a domain comprising an antibody variable region having CD3-binding activity; and (2) a domain comprising an antibody variable region having glypican 3-binding activity, and wherein the VEGF inhibitor is selected from the group consisting of Bevacizumab, Ramucirumab, and Aflibercept.

[0007c]

In yet another aspect, the present disclosure refers to a use of an anti-T cell antigen-binding molecule in the manufacture of a medicament for use in combinatorial therapy for preventing and/or alleviating and/or treating cytokine release syndrome and/or cytokine release, wherein said medicament is to be administered in combination with a vascular epithelial cell growth factor (VEGF) inhibitor, wherein the anti-T cell antigen-binding molecule comprises (1) a domain comprising an antibody variable region having CD3-binding activity; and (2) a domain comprising an antibody variable region having glypican 3-binding activity, and wherein the VEGF inhibitor is selected from the group consisting of Bevacizumab, Ramucirumab, and Aflibercept.

[Technical Problem]

[0008]

In a non-limiting embodiment, the present disclosure relates to combination therapies

[CLAIMS]

1. Use of ~~A pharmaceutical composition comprising~~ an anti-T cell antigen-binding molecule and a vascular epithelial cell growth factor (VEGF) inhibitor in the manufacture of a medicament for combination therapy to prevent and/or alleviate and/or treat cytokine release syndrome and/or cytokine release, wherein the anti-T cell antigen-binding molecule comprises (1) a domain comprising an antibody variable region having CD3-binding activity; and (2) a domain comprising an antibody variable region having glypican 3-binding activity, and wherein the VEGF inhibitor is selected from the group consisting of Bevacizumab, Ramucirumab, and Aflibercept ~~prevents and/or alleviates and/or treats cytokine release syndrome and/or cytokine release~~.

2. Use of an anti-T cell antigen-binding molecule in the manufacture of a first medicament and use of a vascular epithelial cell growth factor (VEGF) inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to prevent and/or alleviate and/or treat cytokine release syndrome and/or cytokine release, wherein the anti-T cell antigen-binding molecule comprises (1) a domain comprising an antibody variable region having CD3-binding activity; and (2) a domain comprising an antibody variable region having glypican 3-binding activity, and wherein the VEGF inhibitor is selected from the group consisting of Bevacizumab, Ramucirumab, and Aflibercept.

3. Use of an anti-T cell antigen-binding molecule in the manufacture of a medicament for use in combinatorial therapy for preventing and/or alleviating and/or treating cytokine release syndrome and/or cytokine release, wherein said medicament is to be administered in combination with a vascular epithelial cell growth factor (VEGF) inhibitor, wherein the anti-T cell antigen-binding molecule comprises (1) a domain comprising an antibody variable region having CD3-binding activity; and (2) a domain comprising an antibody variable region having glypican 3-binding activity, and wherein the VEGF inhibitor is selected from the group consisting of Bevacizumab, Ramucirumab, and Aflibercept.

~~2~~4. The use ~~pharmaceutical composition~~ of any one of claims 1 to 3, wherein the medicament is to be used in combination with the VEGF inhibitor ~~is administered~~ before or simultaneously with administration of the anti-T cell antigen-binding molecule to the subject~~the pharmaceutical composition~~.

~~3~~5. The use ~~pharmaceutical composition~~ of any one of claims 1 ~~or 2~~to 4, wherein the medicament is to be used in combination with~~wherein~~ the VEGF inhibitor ~~is administered~~ 6 days, 5 days, 4 days, 3 days, 2 days, or 1 day before the administration of the anti-T cell antigen-binding molecule to the subject~~the pharmaceutical composition~~, or on the same day as ~~but before~~ the administration of the anti-T cell antigen-binding molecule to the subject~~the pharmaceutical composition~~.

~~4. The pharmaceutical composition of any one of claims 1 to 3, wherein the VEGF inhibitor is selected from the group consisting of an anti-VEGF antigen-binding molecule, an anti-VEGFR1 antigen-binding molecule, an anti-VEGFR2 antigen-binding molecule, a fusion protein comprising a VEGF receptor or a fragment thereof, and a tyrosine kinase inhibitor.~~

~~5. The pharmaceutical composition of any one of claims 1 to 4, wherein the VEGF inhibitor is selected from the group consisting of Bevacizumab, Ramucirumab, and Aflibercept.~~

6. The use~~pharmaceutical composition~~ of any one of claims 1 to 5, wherein the medicament is not to be used in combination with a corticosteroid ~~is not administered~~ before or simultaneously with the administration of the anti-T cell antigen-binding molecule to the subject~~the pharmaceutical composition~~.

7. The use~~pharmaceutical composition~~ of any one of claims 1 to 5, wherein the medicament is to be used further in combination with a corticosteroid ~~is further administered~~ before, simultaneously with, or after the administration of the anti-T cell antigen-binding molecule to the subject~~the pharmaceutical composition~~.

8. The use~~pharmaceutical composition~~ of claim 6 or 7, wherein the corticosteroid is dexamethasone, a pharmaceutically acceptable salt thereof, or a derivative thereof.

~~9. The pharmaceutical composition of any one of claims 1 to 8, wherein the anti-T cell antigen-binding molecule is a bispecific antigen-binding molecule comprising:~~
~~(1) a domain comprising an antibody variable region having T cell receptor complex binding activity; and~~
~~(2) a domain comprising an antibody variable region having cancer antigen-binding activity.~~

9~~10~~. The use~~pharmaceutical composition~~ of any one of claims 1 to 8~~9~~, wherein the anti-T cell antigen-binding molecule is a bispecific antibody further comprising:
~~(1) a domain comprising an antibody variable region having T cell receptor complex-binding activity;~~
~~(2) a domain comprising an antibody variable region having glypican 3-binding activity; and~~
(3) a domain comprising an Fc region with reduced binding activity towards an Fcγ receptor.

10~~11~~. The use~~pharmaceutical composition~~ of any one of claims 1 to ~~10~~9, wherein the anti-T cell antigen-binding molecule is to be administered to the subject ~~which is~~ for treatment of cancer.

11~~12~~. The use~~pharmaceutical composition~~ of claim 10~~11~~, wherein the antitumor effect is enhanced by the combined use as compared to when the anti-T cell antigen-binding molecule~~the pharmaceutical composition~~ or the VEGF inhibitor is to be administered to the subject~~used~~ as a single drug.

12~~13~~. The use~~pharmaceutical composition~~ of any one of claims 1 to 11, wherein the cytokine release syndrome is caused by cytokine release from either or both of a non-tumor tissue and a tumor tissue.

~~14~~13. The use~~pharmaceutical composition~~ of claim ~~13~~12, wherein the tumor tissue comprises GPC3-expressing cells.

~~15. A VEGF inhibitor for preventing and/or alleviating and/or treating cytokine release syndrome and/or cytokine release.~~

14. The use of any one of claims 1 to 13, wherein the anti-T cell antigen-binding molecule is a bispecific antibody that comprises an antibody variable region having binding activity towards glypican 3 and an antibody variable region having binding activity towards CD3ε.

15. The use of any one of claims 1 to 14, wherein the anti-T cell antigen-binding molecule is ERY974.