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]

[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 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.

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.

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

5. The use of any one of claims 1 to 4, wherein the medicament is to be used in

combination with the VEGF inhibitor 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, or on the same day as the administration of the anti-T cell antigen-binding molecule to the subject.

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

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

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

9. The use of any one of claims 1 to 8, wherein the anti-T cell antigen-binding molecule is a bispecific antibody further comprising:
(3) a domain comprising an Fc region with reduced binding activity towards an Fcγ receptor.

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

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

12. The use 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.

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

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.