

CLAIMS

1. Use of an isolated antibody or antigen-binding fragment thereof, specifically binding to CCR8 for use in the manufacture of a medicament for treatment of a tumor or a disease characterized by CCR8 positive cells, wherein a therapeutically effective amount of an anti-CCR8 antibody is to be administered to a human patient having the tumor, wherein the human patient has been diagnosed/stratified as having the tumor based on the level of a biomarker in the tumor or a tumor sample comprising regulatory T cells being higher than or equal to a reference sample or value, where the biomarker is

an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4,

a granzyme or immune cell marker, preferably a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof,

a Treg infiltration marker, preferably CCR8, FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7 or CXCL9,

a T cell marker or cytotoxic T cell marker preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, 4-1BB, OX-40, or GITR,

an interferon or interferon-inducible protein preferably selected from IFN gamma, IL10, IL12p70, IL1beta, IL2 and TNF alpha,

a complement factor, and/or

a serpin.

2. A method for diagnosing/stratifying a subject as having a tumor that is sensitive for treatment with an anti-CCR8 antibody, comprising

a. determining the level of the biomarker in a tumor sample comprising regulatory T cells, wherein the tumor sample has been obtained from the subject,

b. comparing the level of the biomarker with a reference sample or value, and

c. diagnosing/stratifying the subject as having a tumor that is sensitive for treatment with an anti-CCR8 antibody, if the level of the biomarker is higher than or equal to a reference sample or value,

wherein the biomarker is

an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4,

a granzyme or immune cell marker, preferably a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof,

a Treg infiltration marker, preferably CCR8, FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7 or CXCL9,

a T cell marker or cytotoxic T cell marker preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, 4-1BB, OX-40, or GITR,

an interferon or interferon-inducible protein preferably selected from IFN gamma, IL10, IL12p70, IL1beta, IL2 and TNF alpha,

a complement factor, and/or

a serpin.

3. A method to predict or monitor the therapeutic success of a therapy, wherein the therapy comprised the administration of an anti-CCR8 antibody, the method comprising

a. determining the level of a biomarker in a tumor sample, and

b. comparing the level of the biomarker with a reference sample or value,

wherein the biomarker is

an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4,

a granzyme or immune cell marker, preferably a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof,

a Treg infiltration marker, preferably selected from FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7, CXCL9,

a T cell marker or cytotoxic T cell marker, preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, and TNF receptor super family members such as 4-1BB, OX-40, or GITR,

an interferon or interferon-inducible protein, preferably selected from IFN gamma, IL10, IL12p70, IL1beta, IL2 and TNF alpha,

a complement factor, and/or

a serpin.

4. The method according to claim 2 or 3, wherein the biomarker is an immune checkpoint protein.

5. The method according to claim 2 or 3, wherein the biomarker is PD-1, PD-L1, a T cell marker, and/or an interferon or interferon-inducible protein.

6. The method according to claim 2 or 3, wherein the T cell marker is CD8.

7. Use of a molecule binding a biomarker for the manufacture of a diagnostic agent for use in a method of diagnosing/stratifying a subject as having a tumor that is sensitive for treatment with an anti-CCR8 antibody, the method comprising determining the level of the biomarker in a tumor or tumor sample using the molecule binding the biomarker, wherein the biomarker is

an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4,

a granzyme or immune cell marker, preferably a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof,

a Treg infiltration marker, preferably CCR8, FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7 or CXCL9,

a T cell marker or cytotoxic T cell marker preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, 4-1BB, OX-40, or GITR,

an interferon or interferon-inducible protein preferably selected from IFN gamma, IL10, IL12p70, IL1beta, IL2 and TNF alpha,

a complement factor, and/or

a serpin,

and wherein the molecule binding the biomarker is preferably an antibody or antigen-binding fragment, or a conjugate thereof.

8. Use of a molecule binding a biomarker for the manufacture of a diagnostic agent for use in a method to predict or monitor the therapeutic success of a therapy, wherein the therapy comprised the administration of an anti-CCR8 antibody, the method comprising determining the level of the biomarker in a tumor or tumor sample using the molecule binding the biomarker, wherein the biomarker is

an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4,

a granzyme or immune cell marker, preferably a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof,

a Treg infiltration marker, preferably selected from FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7, CXCL9,

a T cell marker or cytotoxic T cell marker, preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, and TNF receptor super family members such as 4-1BB, OX-40, or GITR,

an interferon or interferon-inducible protein, preferably selected from IFN gamma, IL10, IL12p70, IL1beta, IL2 and TNF alpha,

a complement factor, and/or

a serpin,

and wherein the molecule binding the biomarker is preferably an antibody or antigen-binding fragment, or a conjugate thereof.

9. The use according to claim 7 or 8, wherein the molecule binding the biomarker is an anti-PD-1, anti-PD-L1 or anti-CTLA4 antibody such as Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab, Cemiplimab, Dostarlimab or Ipilimumab.

10. The use according to claim 7 or 8, wherein the biomarker is an immune cell marker, and wherein the molecule binding a biomarker is preferably an antibody binding a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof.

11. The use according to claim 7 or 8, wherein the molecule binding the biomarker is a molecule binding a Treg infiltration marker, preferably an antibody binding CCR8, FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7 or CXCL9.

12. The use according to claim 7 or 8, wherein the molecule binding the biomarker is an antibody binding a T cell marker preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, and TNF receptor super family members including 4-1BB, OX-40, or GITR.

13. The use according to claim 7 or 8, wherein the molecule binding the biomarker is an antibody binding an interferon or interferon-inducible protein preferably selected from INF gamma, IL10, IL12p70, IL1beta, IL2 and TNF alpha.

14. The use according to claim 1, 7 or 8, wherein the biomarker is PD-1, PD-L1, a T cell marker, and/or an interferon or interferon-inducible protein.

15. The use according to claim 14, wherein the T cell marker is CD8.

~~1-16. An~~ Use of an anti-CCR8 antibody inducing ADCC and/or ADCP in the manufacture of a medicament for use in the treatment of a tumor, wherein the use comprises administration of medicament is to be administered in combination with a further therapeutically active compound or therapy, wherein a dose of the further therapeutically active compound or therapy is to be administered after the a first dose of the anti-CCR8 antibody medicament, preferably

- a. after the anti-CCR8 antibody has induced an increase of the intra-tumoral CD8 cell to T reg cell ratio at least by a factor of 2, 3, 4 or 5 or
- b. after the anti-CCR8 antibody has depleted at least 40, 45, 50, 55, 60, 65 or 70 % of the intra-tumoral Treg cells.

~~2-17. The anti-CCR8 antibody for~~ use according to claim 16 wherein the further therapeutically active compound or therapy is selected from

an antibody or a small molecule targeting a checkpoint protein, such as PD(L)1 or CTLA-4, a chemotherapeutic agent, preferably a taxane, paclitaxel, doxorubicin, cis-platin, carboplatin, oxaliplatin, or gemcitabine,
an antibody targeting a further chemokine receptor, such as CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CX3CR1 or CXCR1,

an antibody targeting a protein which is specifically expressed by the tumor cells,
an antibody or a small molecule targeting HER2 and/or EGFR,
a targeted kinase inhibitor, such as Sorafeinib, Regorafenib, or MEKi-1,
radiation therapy, and/or

5 depletion of intra-tumoral B cells, preferably CD19+ B cells.

18. The use according to claim 17, wherein the further therapeutically active compound or therapy is selected from an antibody or a small molecule targeting PD(L)1 or CTLA-4, a chemotherapeutic agent, radiation therapy and/or depletion of intra-tumoral B cells.

10 ~~3-19. An Use of an anti-CCR8 antibody inducing ADCC and/or ADCP in the manufacture of a medicament for use in the treatment of a tumor, wherein the medicament is to be administered in combination with the use comprises administration of a further therapeutically active compound or therapy which does not target a checkpoint protein and is selected from~~

15 a chemotherapeutic agent, preferably a taxane, paclitaxel, doxorubicin, cis-platin, carboplatin, oxaliplatin, or gemcitabine,
an antibody targeting a further chemokine receptor, such as CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CX3CR1 or CXCR1,
an antibody targeting a protein which is specifically expressed by the tumor cells,
20 an antibody or a small molecule targeting HER2 and/or EGFR,
a targeted kinase inhibitor, such as Sorafeinib, Regorafenib, or MEKi-1,
radiation therapy, and/or
depletion of intra-tumoral B cells, preferably CD19+ B cells.

25 ~~4-20. The anti-CCR8 antibody for use according to any one of claims 16-19 previous claim, wherein the use comprises furthermore medicament is to be administered in combination with administration of a checkpoint inhibitor such as an anti-PD-1 antibody, an anti-PD-L1 antibody or a CTLA4 antibody.~~

21. The use according to claim 19, wherein the further therapeutically active compound or therapy is selected from a chemotherapeutic agent, radiation therapy and/or depletion of intra-tumoral B cells

30 ~~22. 5. An Use of an anti-CCR8 antibody inducing ADCC and/or ADCP in the manufacture of a medicament for use in the treatment of a tumor, wherein only a single dose of the anti-CCR8 antibody is to be administered to a subject, such that no further dose of the same or a different anti-CCR8 antibody is to be administered to the subject.~~

6. A biomarker for use in a method for diagnosing/stratifying a subject as having a tumor that is sensitive for treatment with an anti-CCR8 antibody, the use comprising

- a. determining the level of the biomarker in a tumor or tumor sample comprising regulatory T cells,
- b. comparing the level of the biomarker with a reference sample or value, and
- c. diagnosing/stratifying a subject as having a tumor that is sensitive for treatment with an anti-CCR8 antibody, if the level of the biomarker is higher than or equal to a reference sample or value,

wherein the biomarker is

- d. an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4,
- e. a granzyme or immune cell marker, preferably a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof,
- f. a Treg infiltration marker, preferably CCR8, FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7 or CXCL9,
- g. a T cell marker or cytotoxic T cell marker preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, 4-1BB, OX-40, or GITR,
- h. an interferon or interferon-inducible protein preferably selected from IFN gamma, IL10, IL12p70, IL1beta, IL2 and TNF alpha,
- i. a complement factor, and/or
- j. a serpin.

7. Use of a biomarker to predict or monitor the therapeutic success of a therapy comprising the administration of an anti-CCR8 antibody, the use comprising

- a. determining the level of the biomarker in a tumor sample, and
- b. comparing the level of the biomarker with a reference sample or value,

wherein the biomarker is

- c. an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4,
- d. a granzyme or immune cell marker, preferably a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof,
- e. a Treg infiltration marker, preferably selected from FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7, CXCL9,
- f. a T cell marker or cytotoxic T cell marker, preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, and TNF receptor super family members such as 4-1BB, OX-40, or GITR,

- g.—an interferon-inducible protein, preferably selected from IFN gamma, IL10, IL12p70, IL1beta, IL2 and TNF alpha,
- h.—a complement factor, and/or
- i.—a serpin.

8.—The biomarker for use according to claim 6, or the use of the biomarker according to claim 7, wherein the biomarker is an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4.

9.—A molecule binding a biomarker for use in a method for diagnosing/stratifying a subject as having a tumor that is sensitive for treatment with an anti-CCR8 antibody, the use comprising determining the level of the biomarker in a tumor or tumor sample using the molecule binding the biomarker, wherein the biomarker is

- a.—an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4,
 - b.—a granzyme or immune cell marker, preferably a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof,
 - c.—a Treg infiltration marker, preferably CCR8, FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7 or CXCL9,
 - d.—a T cell marker or cytotoxic T cell marker preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, 4-1BB, OX-40, or GITR,
 - e.—an interferon or interferon-inducible protein preferably selected from IFN gamma, IL10, IL12p70, IL1beta, IL2 and TNF alpha,
 - f.—a complement factor, and/or
 - g.—a serpin,
- and wherein the molecule binding the biomarker is preferably an antibody or antigen-binding fragment, or a conjugate thereof.

10.—Use of a molecule binding a biomarker to predict or monitor the therapeutic success of a therapy comprising the administration of an anti-CCR8 antibody, the use comprising determining the level of the biomarker in a tumor or tumor sample using the molecule binding the biomarker, wherein the biomarker is

- a.—an immune checkpoint protein, preferably PD-1, PD-L1 or CTLA4,
- b.—a granzyme or immune cell marker, preferably a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof,
- c.—a Treg infiltration marker, preferably selected from FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7, CXCL9,

d. ~~a T cell marker or cytotoxic T cell marker, preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, and TNF receptor super family members such as 4-1BB, OX-40, or GITR,~~
e. ~~an interferon-inducible protein, preferably selected from IFN-gamma, IL-10, IL-12p70, IL-1beta, IL-2 and TNF-alpha,~~
f. ~~a complement factor, and/or~~
g. ~~a serpin,~~
and wherein the molecule binding the biomarker is preferably an antibody or antigen-binding fragment, or a conjugate thereof.

11. ~~The molecule binding a biomarker for use according to claim 9 or the use of a molecule binding a biomarker according to claim 10, wherein the molecule binding the biomarker is an anti-PD-1, anti-PD-L1 or anti-CTLA4 antibody such as Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab, Cemiplimab, Dostarlimab or Ipilimumab.~~

12. ~~The molecule binding a biomarker for use according to claim 8 or the use of a molecule binding a biomarker according to claim 9, wherein the biomarker is an immune cell marker, and wherein the molecule binding a biomarker is preferably an antibody binding a marker for lymphocytes, effector cells, T cells, cytotoxic T cells, macrophage cells, M1 macrophage cells, M2 macrophage cells, B cells, NK cells, or a combination thereof.~~

13. ~~The molecule binding a biomarker for use or the use of a molecule binding a biomarker according to claim 12, wherein the molecule binding the biomarker is a molecule binding a Treg infiltration marker, preferably an antibody binding CCR8, FOXP3, ICOS, CCR4, TIGIT, P2RY10, CD80, TNFRSF9, CD3(G), SLAMF1, IL7R, IL2RB, CTLA4, CD5, ITK, IL2RA, LAX1, IKZF3, GBP5, CXCR6, SIRPG, CD2, CSF2RB, SLAMF7 or CXCL9.~~

14. ~~The molecule binding a biomarker for use or the use of a molecule binding a biomarker according to claim 12, wherein the molecule binding the biomarker is an antibody binding a T-cell marker preferably selected from CD3, CD4, CD8, CD25, CXCR3, CCR5, and TNF receptor super family members including 4-1BB, OX-40, or GITR.~~

15. ~~The molecule binding a biomarker for use according to claim 9 or the use of a molecule binding a biomarker according to claim 10, wherein the molecule binding the biomarker is an antibody binding an interferon or interferon-inducible protein preferably selected from IFN-gamma, IL-10, IL-12p70, IL-1beta, IL-2 and TNF-alpha.~~