The immuno-suppressive tumor microenvironment poses a major hurdle for anti-tumor immunity and immunotherapeutic treatment approaches (Beatty, G. L., et al. Science 331 (2011) 1612-1616).

Summary

The present inventors have found that anti-ANG2 antibodies enhance the efficacy of CD40 agonists to treat cancers or delay progression of a tumor or the survival of a patient afflicted with cancer e.g. with a solid tumor. The delay of progression, the longer survival as well as the potential of reduced doses with lower risk of side effects represent a major benefit for patients.

Surprisingly a treatment of tumors with anti-ANG2 antibodies in combination with CD40 agonists showed strong synergistic effect on the time to tumor progression and the time of survival (whereas a combination of anti-VEGF antibodies in combination with CD40 agonists only showed small effects).

The disclosure relates to an antibody that binds to human angiopoietin 2 (ANG-2) wherein the antibody is administered in combination with a CD40 agonist a) for use in treating or delaying progression of cancer, or b) for use in prolonging the survival of a patient suffering from cancer, or c) for use in stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

The disclosure also relates to a CD40 agonist wherein the a CD40 agonist is administered in combination with an antibody that binds to human angiopoietin 2 (ANG-2) a) for use in treating or delaying progression of cancer, or b) for use in prolonging the survival of a patient suffering from cancer, or c) for use in stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

The disclosure also provides a method for a) treating or delaying progression of cancer, or b) prolonging the survival of a patient suffering from cancer, or c) stimulating an immune response or function, such as T cell activity (in

cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

Another aspect of the disclosure is an antibody that binds to human angiopoietin 2 (ANG-2) wherein the antibody is to be administered in combination with an agonistic CD40 antibody

a) for use in treating or delaying progression of cancer, or

b) for use in prolonging the survival of a patient suffering from cancer.

The disclosure also relates to an antibody that binds to human angiopoietin 2 (ANG-2) in combination with a CD40 agonist in the manufacture of a medicament for
a) for use in treating or delaying progression of cancer, or
b) for use in prolonging the survival of a patient suffering from cancer, or
c) for use in stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or
d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

The disclosure also provides a method for a) treating or delaying progression of cancer, or b) prolonging the survival of a patient suffering from cancer, or c) stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2), wherein the method comprises the step of administering an effective amount of an anti-ANG2 antibody and an effective amount of a CD40 agonist to a patient in need thereof.

The disclosure also relates to an antibody that binds to human angiopoietin 2 (ANG-2) and a CD40 agonist for use in combination a) for treating or delaying progression of cancer, or b) for prolonging the survival of a patient suffering from cancer, or c) for stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) for rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

Patent Claims

1. An antibody that binds to human angiopoietin 2 (ANG-2) wherein the antibody is to be administered in combination with an agonistic CD40 antibody

a) for use in treating or delaying progression of cancer, or

b) for use in prolonging the survival of a patient suffering from cancer.

2. The anti-ANG2 antibody for use according to claim 1, wherein the anti-ANG2 antibody is human or humanized.

3. The anti-ANG2 antibody for use according to any one of the preceding claims, wherein the anti-ANG2 antibody is an IgG antibody.

4. The antibody that binds to human ANG-2 according to any one of claims 1 to 3,
i) wherein the anti-ANG2 antibody comprises
(a) a heavy chain variable domain amino acid sequence of SEQ ID NO:1 and a light chain variable domain amino acid sequence of SEQ ID NO:2; or
(b) a heavy chain variable domain amino acid sequence of SEQ ID NO:3 and a light chain variable domain amino acid sequence of SEQ ID NO:4;
and
ii) wherein the agonistic CD40 antibody comprises
(a) a heavy chain variable domain amino acid sequence of SEQ ID NO: 5 and a light chain variable domain amino acid sequence of SEQ ID NO: 6; or
(b) a heavy chain variable domain amino acid sequence of SEQ ID NO: 7 and a light chain variable domain amino acid sequence of SEQ ID NO: 8.

5. The antibody that binds to human ANG-2 according to any one of claims 1 to 3,
i) wherein the anti-ANG2 antibody comprises
a heavy chain variable domain amino acid sequence of SEQ ID NO:1 and a light chain variable domain amino acid sequence of SEQ ID NO:2; or
and
ii) wherein the agonistic CD40 antibody comprises
a heavy chain variable domain amino acid sequence of SEQ ID NO: 5 and a light chain variable domain amino acid sequence of SEQ ID NO: 6.

6. The anti-ANG2 antibody for use according to any one of claims 1 to 3, wherein the anti-ANG2 antibody is a bispecific antibody that binds to human ANG-2 and that binds to human VEGF.

7. The antibody that binds to human ANG-2 according to claims 4 or 6,
i) wherein the bispecific antibody that binds to human ANG-2 and that binds to human VEGF comprises
a heavy chain variable domain amino acid sequence of SEQ ID NO:1 and a light chain variable domain amino acid sequence of SEQ ID NO:2; and
a heavy chain variable domain amino acid sequence of SEQ ID NO:9 and a light chain variable domain amino acid sequence of SEQ ID NO:10;
and

ii) wherein the agonistic CD40 antibody comprises
a heavy chain variable domain amino acid sequence of SEQ ID NO: 5 and a light chain variable domain amino acid sequence of SEQ ID NO: 6.

8. The antibody that binds to human ANG-2 according to claims 4 or 6,
i) wherein the bispecific antibody that binds to human ANG-2 and that binds to human VEGF comprises the amino acid sequences of SEQ ID NO: 11, of SEQ ID NO: 12, of SEQ ID NO: 13, and of SEQ ID NO: 14; and

ii) wherein the agonistic CD40 antibody comprises
a heavy chain variable domain amino acid sequence of SEQ ID NO: 5 and a light chain variable domain amino acid sequence of SEQ ID NO: 6.