

SUMMARY

The above-mentioned object and other objects are achieved by the teaching of the present invention.

First example of the disclosure: An anti-CECAM6 antibody

5 In a first aspect, the present disclosure relates to an anti-CECAM6 antibody comprising an IgG1 Fc region lacking the glycans attached to the conserved N-linked site in the CH2 domains of the Fc region, wherein said IgG1 Fc region comprises at least the amino acid substitutions L234A and L235A, as numbered according to the EU index of Kabat.

10 In another aspect, the disclosure refers to an anti-CECAM6 antibody comprising an IgG1 Fc region, wherein said IgG1 Fc region comprises at least the amino acid substitutions N297A, L234A, and L235A as numbered according to the EU index of Kabat.

15 In yet another aspect, the disclosure refers to an anti-CECAM6 antibody, wherein said antibody comprises: a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 71, and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 72. In a further aspect, the disclosure refers to an anti-CECAM6 antibody consisting of: a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 71, and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 72.

20 In certain examples of the first example the disclosure provides an anti-CECAM6 antibody comprising an IgG1 Fc region, wherein said IgG1 Fc region comprises an amino acid substitution N297A, N297G, or N297Q as numbered according to the EU index of Kabat.

In certain examples of the first example the disclosure provides an anti-CECAM6 antibody comprising an IgG1 Fc region, wherein said IgG1 Fc region comprises an amino acid substitution N297A, N297G, or N297Q and at least the amino acid substitutions L234A and L235A, as numbered according to the EU index of Kabat.

25 In certain examples of the first example the disclosure provides an anti-CECAM6 antibody comprising an IgG1 Fc region, wherein said IgG1 Fc region comprises at least the amino acid substitutions N297A, L234A, and L235A, as numbered according to the EU index of Kabat.

30 In certain examples of the first example the disclosure provides an anti-CECAM6 antibody comprising an IgG1 Fc region, wherein said IgG1 Fc region comprises the amino acid substitutions N297A, L234A, and L235A, as numbered according to the EU index of Kabat.

In certain examples of the first example the anti-CECAM6 antibody mentioned supra competes for CEACAM6 binding with an antibody comprising a heavy chain variable region (VH) comprising the amino acid sequence of Seq ID No: 63 and a light chain variable region (VL) comprising the amino acid sequence of Seq ID No: 67.

In certain examples of the first example the anti-CECAM6 antibody mentioned supra comprises: a heavy chain variable region H-CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a heavy chain variable region H-CDR2 comprising the amino acid sequence of SEQ ID NO: 65, a heavy chain variable region H-CDR3 comprising the amino acid sequence of SEQ ID NO: 66, a light chain variable region L-CDR1 comprising the amino acid sequence of SEQ ID NO: 68, a light chain variable region L-CDR2 comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region L-CDR3 comprising the amino acid sequence of SEQ ID NO: 70.

In certain examples of the first example the anti-CECAM6 antibody mentioned supra comprises: a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 63, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 67.

5 In certain examples of the first example the anti-CECAM6 antibody mentioned supra comprises: a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 71, and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 72.

In certain examples the disclosure provides an anti-CECAM6 antibody comprising a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 71, and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 72.

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Further examples of the disclosure:

15 In one aspect, the disclosure provides a nucleic acid that encodes the anti-CECAM6 antibody of as disclosed herein. In another aspect, the disclosure provides an isolated cell expressing the anti-CECAM6 antibody and /or comprising the nucleic acid as disclosed herein. In yet another aspect, the disclosure provides a method of producing the anti-CECAM6 antibody as disclosed herein comprising culturing of the cell as disclosed herein and purification of the antibody.

In a further example the disclosure provides a nucleic acid that encodes the anti-CECAM6 antibody of the first example, and a vector comprising said nucleic acid.

20 In a further example the disclosure provides an isolated cell expressing the anti-CECAM6 antibody of the first example. In preferred examples this cell is a prokaryotic or a eukaryotic cell.

In a further example the disclosure provides a method of producing the anti-CECAM6 antibody of the first example.

25 In a further aspect, the disclosure provides an anti-CECAM6 antibody as disclosed herein for use as a medicament. In another aspect, the disclosure provides a use of the anti-CECAM6 antibody as disclosed herein in the manufacture of a medicament for the treatment of a cancer.

30 In a further example the disclosure provides an anti-CECAM6 antibody of the first example for use as a medicament, in particular for use as a medicament for the treatment of cancer. In certain examples of this example a method is provided for treating cancer associated with the undesired presence of CEACAM6, comprising administering to a subject in need thereof an effective amount of the anti-CECAM6 antibody of the first example.

In a further example the disclosure provides an anti-CEACAM6 antibody of the first example for use in simultaneous, separate, or sequential combination with an anti-PD-1 antibody or an anti-PD-L1 antibody in the treatment of cancer. In certain examples the anti-PD-1 antibody is
5 nivolumab, or pembrolizumab, and the anti-PD-L1 antibody is atezolizumab, avelumab, or durvalumab. In certain examples of this example a method of treating cancer is provided comprising administering to a patient in need thereof an effective amount of an anti-CEACAM6 antibody of the first example in simultaneous, separate, or sequential combination with an anti-PD-1 antibody or an anti-PD-L1 antibody, preferably the anti-PD-1 antibody is nivolumab, or
10 pembrolizumab, and the anti-PD-L1 antibody is atezolizumab, avelumab, or durvalumab.

In a further example the disclosure provides an anti-CEACAM6 antibody of the first example for use in simultaneous, separate, or sequential combination with an anti-TIM-3 antibody in the treatment of cancer. In certain examples the anti-TIM-3 antibody is cobolimab, MBG-453, BMS-986258, Sym-023, LY-3321367 or INCAGN-2390. In certain examples of this example a method of treating cancer is provided comprising administering to a patient in need thereof an effective amount of the anti-CEACAM6 antibody of the first example in simultaneous, separate, or sequential combination with an anti-TIM-3 antibody, preferably the anti-TIM-3 antibody is cobolimab, MBG-453, BMS-986258, Sym-023, LY-3321367 or INCAGN-2390.

In another aspect, the disclosure provides a pharmaceutical composition comprising the anti-CECAM6 antibody as disclosed herein. In a further aspect the disclosure provides a pharmaceutical composition comprising the anti-CECAM6 antibody of the first example.

DESCRIPTION OF THE FIGURES

Figure 1: TNF-alpha plasma levels at different time points after start of the i.v. infusion of the anti-CEACAM6 antibody TPP-3310 to cancer patients. Three patients per dose cohort have been treated with either 2.5 mg, 5 mg, 10 mg or 30 mg of TPP-3310 in the clinical formulation over 1 hour. Mean values plus standard deviations are given. X-axis: Time after start of infusion in hours; Y-axis: Concentration of TNF-alpha in plasma [pg/mL]

Figure 2: IL-6 plasma levels at different time points after start of the i.v. infusion of the anti-CEACAM6 antibody TPP-3310 to cancer patients. Three patients per dose cohort have been infused with either 2.5 mg, 5 mg, 10 mg or 30 mg of TPP-3310 in the clinical formulation over 1 hour. Mean values plus standard deviations are given. X-axis: Time after start of infusion in hours; Y-axis: Concentration of IL-6 in plasma [pg/mL]

Figure 3: IL-10 plasma levels at different time points after start of the i.v. infusion of the anti-CEACAM6 antibody TPP-3310 to cancer patients. Three patients per dose cohort have been infused with either 2.5 mg, 5 mg, 10 mg or 30 mg of TPP-3310 in the clinical formulation over 1 hour. Mean values plus standard deviations are given. X-axis: Time after start of infusion in hours; Y-axis: Concentration of IL-10 in plasma [pg/mL]

Figure 4: Plasma levels of myeloperoxidase (MPO) at different time points after start of the i.v. infusion of the anti-CEACAM6 antibody TPP-3310 to cancer patients. Three patients per dose cohort have been infused with either 2.5 mg, 5 mg, 10 mg or 30 mg of TPP-3310 in the clinical formulation over 1 hour. Relative values in comparison to pre-treatment are given as percentage mean values plus standard deviations. X-axis: Time after start of infusion in hours; Y-axis: Concentration of MPO in plasma [% vs. 0h pre-treatment levels]

Figure 5. Neutrophil count of patients treated at 30 mg TPP-3310 at selected time points. A value of < 0.5 /nL is considered a severe neutrophil count decrease according to CTCAE criteria.

CLAIMS

1. An anti-CECAM6 antibody comprising an IgG1 Fc region lacking the glycans attached to the conserved N-linked site in the CH2 domains of the Fc region, wherein said IgG1 Fc region comprises at least the amino acid substitutions L234A and L235A, as numbered according to the EU index of Kabat.
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2. The anti-CECAM6 antibody of claim 1, wherein the IgG1 Fc region comprises an amino acid substitution N297A, N297G, or N297Q as numbered according to the EU index of Kabat.
3. An anti-CECAM6 antibody comprising an IgG1 Fc region, wherein said IgG1 Fc region comprises at least the amino acid substitutions N297A, L234A, and L235A as numbered according to the EU index of Kabat.
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4. The anti-CECAM6 antibody of any of claims 1 to 3, wherein said antibody competes for CECAM6 binding with an antibody comprising a heavy chain variable region (VH) comprising the amino acid sequence of Seq ID No: 63 and a light chain variable region (VL) comprising the amino acid sequence of Seq ID No: 67.
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5. The anti-CECAM6 antibody of any of claims 1 to 4, wherein said antibody comprises:
 - a. a heavy chain variable region H-CDR1 comprising the amino acid sequence of SEQ ID NO: 64,
 - b. a heavy chain variable region H-CDR2 comprising the amino acid sequence of SEQ ID NO: 65,
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 - c. a heavy chain variable region H-CDR3 comprising the amino acid sequence of SEQ ID NO: 66,
 - d. a light chain variable region L-CDR1 comprising the amino acid sequence of SEQ ID NO: 68,
 - e. a light chain variable region L-CDR2 comprising the amino acid sequence of SEQ ID NO: 69, and
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 - f. a light chain variable region L-CDR3 comprising the amino acid sequence of SEQ ID NO: 70.
6. The anti-CECAM6 antibody of any of claims 1 to 4, wherein said antibody comprises:
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 - a. a heavy chain variable region H-CDR1 amino acid sequence of SEQ ID NO: 64,
 - b. a heavy chain variable region H-CDR2 amino acid sequence of SEQ ID NO: 65,
 - c. a heavy chain variable region H-CDR3 amino acid sequence of SEQ ID NO: 66,

- d. a light chain variable region L-CDR1 amino acid sequence of SEQ ID NO: 68,
 - e. a light chain variable region L-CDR2 amino acid sequence of SEQ ID NO: 69,
and
 - f. a light chain variable region L-CDR3 amino acid sequence of SEQ ID NO: 70.
- 5 7. The anti-CECAM6 antibody of any of claims 1 to 6, wherein said antibody comprises:
- a. a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 63, and
 - b. a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 67.
- 10 8. The anti-CECAM6 antibody of any of claims 1 to 7, wherein said antibody comprises:
- a. a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 71, and
 - b. a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 72.
- 15 9. An anti-CECAM6 antibody, wherein said antibody comprises:
- a. a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 71, and
 - b. a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 72.
- 20 10. An anti-CECAM6 antibody consisting of:
- a. a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 71, and
 - b. a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 72.
- 25 11. The anti-CECAM6 antibody of any of claims 1 to 10, wherein said antibody specifically binds to CECAM6 comprising the amino acid sequence of SEQ ID NO: 75.
- 30 12. The anti-CECAM6 antibody of any of claims 1 to 11, wherein said antibody specifically binds to CECAM6 domain 1 comprising the amino acids 35 – 142 of SEQ-ID NO:75.
13. A nucleic acid that encodes the anti-CECAM6 antibody of any of claims 1 to 12.
14. An isolated cell expressing the anti-CECAM6 antibody of any of claims 1 to 12 and /or comprising the nucleic acid of claim 13.
15. A method of producing the anti-CECAM6 antibody of any of claims 1 to 12 comprising culturing of the cell of claim 14 and purification of the antibody.
16. An anti-CECAM6 antibody of any of claims 1 to 12 for use as a medicament.
17. Use of the anti-CECAM6 antibody of any of claims 1 to 12 in the manufacture of a medicament for the treatment of a cancer.

18. A pharmaceutical composition comprising the anti-CECAM6 antibody of any of claims 1 to 12.
19. The use of claim 17 in simultaneous, separate, or sequential combination with an anti-TIM-3 antibody in the treatment of cancer.
- 5 20. The use of claim 19, wherein the anti-TIM-3 antibody is cobolimab, MBG-453, BMS-986258, Sym-023, LY-3321367 or INCAGN-2390.