Proposed Amended Claims

1. (**Currently Amended**) The use of **both:**

(a) an anti-IL-6R antibody or antigen-binding fragment thereof; and

(b) an antigen-specific binding protein that specifically binds VEGF;

in the manufacture of a pharmaceutical composition for use in inhibiting or attenuating the growth of an anti-VEGF-resistant tumor in a subject, wherein the tumor exhibits increased IL-6/STAT3 signaling.

2. The use of claim 1, wherein the anti-IL-6R antibody or antigen-specific binding fragment thereof comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) wherein the HCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:4, 5, and 6; and wherein LCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:7, 8 and 9.

3. The use of claim 2, wherein the HCVR comprises the complementarity determining regions (CDRs) of SEQ ID NO:2, and wherein the LCVR comprises the CDRs of SEQ ID NO:3.

4. The use of any one of claims 1 to 3, further comprising an EGFR antagonist.

5. The use of claim 4, wherein the EGFR antagonist is selected from the group consisting of an anti-EGFR antibody, an anti-EGFRvIII antibody, an anti-ErbB2 antibody, an anti-ErbB3 antibody, and an anti-ErbB4 antibody.

6. The use of claim 1, wherein the antigen-specific binding protein is a fusion protein comprising Ig domain 2 of VEGFR1, Ig domain 3 of VEGFR2, and a multimerizing domain.

7. The use of claim 6, wherein the Ig domain 2 of VEGFR1 comprises amino acids 27 to 129 of SEQ ID NO:11, the Ig domain 3 of VEGFR2 comprises amino acids 130 to 231 of SEQ ID NO:11, and the multimerizing domain comprises amino acids 232 to 457 of SEQ ID NO:11.

8. (**Currently Amended**) The use of **all three of:**

(a) an anti-IL-6R antibody or antigen-binding fragment thereof**;**

(b) an antigen-specific binding protein that specifically binds VEGF; and

(c) an EGFR antagonist selected from the group consisting of an anti-EGFR antibody, an anti-EGFRvIII antibody, an anti-ErbB2 antibody, an anti-ErbB3 antibody, and an anti-ErbB4 antibody;

in the manufacture of a pharmaceutical composition for inhibiting or attenuating the growth of an anti-VEGF-resistant tumor in a subject wherein the tumor exhibits increased IL-6/STAT3 signaling,

wherein the anti-IL-6R antibody or antigen-specific binding fragment thereof comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR),

wherein the HCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:4, 5, and 6; and wherein LCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:7, 8 and 9.

9. (**Cancelled**) ~~The use of claim 8, further comprising an EGFR antagonist selected from the group consisting of an anti-EGFR antibody, an anti-EGFRvIII antibody, an anti-ErbB2 antibody, an anti-ErbB3 antibody, and an anti-ErbB4 antibody.~~

10. (**Cancelled**) ~~The use of claim 8, further comprising an antigen-specific binding protein that specifically binds VEGF.~~

11. (**Currently Amended**) The use of claim **8**~~10~~, wherein the antigen-specific binding protein is a fusion protein comprising Ig domain 2 of VEGFR1, Ig domain 3 of VEGFR2, and a multimerizing domain.

12. The use of claim 11, wherein the Ig domain 2 of VEGFR1 comprises amino acids 27 to 129 of SEQ ID NO:11, the Ig domain 3 of VEGFR2 comprises amino acids 130 to 231 of SEQ ID NO:11, and the multimerizing domain comprises amino acids 232 to 457 of SEQ ID NO:11.

CLAIMS

1. The use of an anti-IL-6R antibody or antigen-binding fragment thereof; and an antigen-specific binding protein that specifically binds VEGF; in the manufacture of a pharmaceutical composition for use in inhibiting or attenuating the growth of an anti-VEGF-resistant tumor in a subject wherein the tumor exhibits increased IL-6/STAT3 signaling.

2. The use of claim 1, wherein the anti-IL-6R antibody or antigen-specific binding fragment thereof comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) wherein the HCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:4, 5, and 6; and wherein LCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:7, 8 and 9.

3. The use of claim 2, wherein the HCVR comprises the complementarity determining regions (CDRs) of SEQ ID NO:2, and wherein the LCVR comprises the CDRs of SEQ ID NO:3.

4. The use of any one of claims 1 to 3, further comprising an EGFR antagonist.

5. The use of claim 4, wherein the EGFR antagonist is selected from the group consisting of an anti-EGFR antibody, an anti-EGFRvIII antibody, an anti-ErbB2 antibody, an anti-ErbB3 antibody, and an anti-ErbB4 antibody.

6. The use of claim 1, wherein the antigen-specific binding protein is a fusion protein comprising Ig domain 2 of VEGFR1, Ig domain 3 of VEGFR2, and a multimerizing domain.

7. The use of claim 6, wherein the Ig domain 2 of VEGFR1 comprises amino acids 27 to 129 of SEQ ID NO:11, the Ig domain 3 of VEGFR2 comprises amino acids 130 to 231 of SEQ ID NO:11, and the multimerizing domain comprises amino acids 232 to 457 of SEQ ID NO:11.

8. The use of an anti-IL-6R antibody or antigen-binding fragment thereof in the manufacture of a pharmaceutical composition for inhibiting or attenuating the growth of an anti-VEGF-resistant tumor in a subject wherein the tumor exhibits increased IL-6/STAT3 signaling,

wherein the anti-IL-6R antibody or antigen-specific binding fragment thereof comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR),

wherein the HCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:4, 5, and 6; and wherein LCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:7, 8 and 9.

9. The use of claim 8, further comprising an EGFR antagonist selected from the group consisting of an anti-EGFR antibody, an anti-EGFRvIII antibody, an anti-ErbB2 antibody, an anti-ErbB3 antibody, and an anti-ErbB4 antibody.

10. The use of claim 8, further comprising an antigen-specific binding protein that specifically binds VEGF.

11. The use of claim 10, wherein the antigen-specific binding protein is a fusion protein comprising Ig domain 2 of VEGFR1, Ig domain 3 of VEGFR2, and a multimerizing domain.

12. The use of claim 11, wherein the Ig domain 2 of VEGFR1 comprises amino acids 27 to 129 of SEQ ID NO:11, the Ig domain 3 of VEGFR2 comprises amino acids 130 to 231 of SEQ ID NO:11, and the multimerizing domain comprises amino acids 232 to 457 of SEQ ID NO:11.

CLAIMS

1. The use of both:

(a) an anti-IL-6R antibody or antigen-binding fragment thereof; and

(b) an antigen-specific binding protein that specifically binds VEGF;

in the manufacture of a pharmaceutical composition for use in inhibiting or attenuating the growth of an anti-VEGF-resistant tumor in a subject,

wherein the tumor exhibits increased IL-6/STAT3 signaling.

2. The use of claim 1, wherein the anti-IL-6R antibody or antigen-specific binding fragment thereof comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) wherein the HCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:4, 5, and 6; and wherein LCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:7, 8 and 9.

3. The use of claim 2, wherein the HCVR comprises the complementarity determining regions (CDRs) of SEQ ID NO:2, and wherein the LCVR comprises the CDRs of SEQ ID NO:3.

4. The use of any one of claims 1 to 3, further comprising an EGFR antagonist.

5. The use of claim 4, wherein the EGFR antagonist is selected from the group consisting of an anti-EGFR antibody, an anti-EGFRvIII antibody, an anti-ErbB2 antibody, an anti-ErbB3 antibody, and an anti-ErbB4 antibody.

6. The use of claim 1, wherein the antigen-specific binding protein is a fusion protein comprising Ig domain 2 of VEGFR1, Ig domain 3 of VEGFR2, and a multimerizing domain.

7. The use of claim 6, wherein the Ig domain 2 of VEGFR1 comprises amino acids 27 to 129 of SEQ ID NO:11, the Ig domain 3 of VEGFR2 comprises amino acids 130 to 231 of SEQ ID NO:11, and the multimerizing domain comprises amino acids 232 to 457 of SEQ ID NO:11.

8. The use of all three of:

(a) an anti-IL-6R antibody or antigen-binding fragment thereof;

(b) an antigen-specific binding protein that specifically binds VEGF; and

(c) an EGFR antagonist selected from the group consisting of an anti-EGFR antibody, an anti-EGFRvIII antibody, an anti-ErbB2 antibody, an anti-ErbB3 antibody, and an anti-ErbB4 antibody;

in the manufacture of a pharmaceutical composition for inhibiting or attenuating the growth of an anti-VEGF-resistant tumor in a subject wherein the tumor exhibits increased IL-6/STAT3 signaling,

wherein the anti-IL-6R antibody or antigen-specific binding fragment thereof comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR),

wherein the HCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:4, 5, and 6; and wherein LCVR comprises CDRs having the amino acid sequences of SEQ ID NOs:7, 8 and 9.

9. The use of claim 8, wherein the antigen-specific binding protein is a fusion protein comprising Ig domain 2 of VEGFR1, Ig domain 3 of VEGFR2, and a multimerizing domain.

10. The use of claim 9, wherein the Ig domain 2 of VEGFR1 comprises amino acids 27 to 129 of SEQ ID NO:11, the Ig domain 3 of VEGFR2 comprises amino acids 130 to 231 of SEQ ID NO:11, and the multimerizing domain comprises amino acids 232 to 457 of SEQ ID NO:11.