

Claims

1. Use of an antibody or functional part thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5 in the manufacture of a medicament for the treatment of cancer in a subject, wherein the subject has received or is receiving a human topoisomerase I inhibitor.
2. Use of a human topoisomerase I inhibitor in the manufacture of a medicament for the treatment of cancer in a subject, wherein the subject has received or is receiving an antibody or functional part thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5.
3. Use of an antibody or functional part thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5, and a human topoisomerase I inhibitor in the manufacture of a medicament for the combination therapy of cancer in a subject.
4. The use according to any one of the preceding claims, wherein the cancer is colorectal, pulmonary, gastrointestinal or ovarian cancer.
5. The use according to any one of the preceding claims, wherein the cancer is colorectal cancer.
6. The antibody or functional part thereof according to any of the preceding claims, wherein the variable domain that binds an extracellular part of EGFR comprises a heavy chain variable region comprising the CDR1, CDR2 and CDR3 sequences of a variable region selected from the group consisting of MF3370 (SEQ ID NO: 87); MF3755 (SEQ ID NO: 89); MF4280 (SEQ ID NO: 91) or MF4289 (SEQ ID NO: 93) and wherein the variable domain that binds an extracellular part of LGR5 comprises a heavy chain variable region comprising the CDR1, CDR2 and CDR3 sequences of a variable region selected from the group consisting of MF5790 (SEQ ID NO: 95); MF5803 (SEQ ID NO: 97); MF5805 (SEQ ID NO: 99); MF5808 (SEQ ID NO: 101); MF5809 (SEQ ID NO: 103); MF5814 (SEQ ID NO: 105); MF5816 (SEQ ID NO: 107); MF5817 (SEQ ID NO: 109); or MF5818 (SEQ ID NO: 111).
7. The antibody or functional part thereof according to any of the preceding claims, wherein the variable domain that binds an extracellular part of EGFR comprises a heavy chain variable region comprising:
-a CDR1 having SEQ ID NO: 11, CDR2 having SEQ ID NO: 12, and CDR3 having SEQ ID NO: 14;

-a CDR1 having SEQ ID NO: 17, CDR2 having SEQ ID NO: 19, and CDR3 having SEQ ID NO: 21;

-a CDR1 having SEQ ID NO: 23, CDR2 having SEQ ID NO: 25, and CDR3 having SEQ ID NO: 27; or

-a CDR1 having SEQ ID NO: 29, CDR2 having SEQ ID NO: 30, and CDR3 having SEQ ID NO: 32;

and wherein the variable domain that binds an extracellular part of LGR5 comprises a heavy chain variable region comprising:

-a CDR1 having SEQ ID NO: 34, CDR2 having SEQ ID NO: 36, and CDR3 having SEQ ID NO: 38;

-a CDR1 having SEQ ID NO: 40, CDR2 having SEQ ID NO: 41, and CDR3 having SEQ ID NO: 43;

-a CDR1 having SEQ ID NO: 46, CDR2 having SEQ ID NO: 48, and CDR3 having SEQ ID NO: 50;

-a CDR1 having SEQ ID NO: 53, CDR2 having SEQ ID NO: 36, and CDR3 having SEQ ID NO: 55;

-a CDR1 having SEQ ID NO: 57, CDR2 having SEQ ID NO: 59, and CDR3 having SEQ ID NO: 61;

-a CDR1 having SEQ ID NO: 63, CDR2 having SEQ ID NO: 65, and CDR3 having SEQ ID NO: 67;

-a CDR1 having SEQ ID NO: 69, CDR2 having SEQ ID NO: 71, and CDR3 having SEQ ID NO: 73;

-a CDR1 having SEQ ID NO: 75, CDR2 having SEQ ID NO: 76, and CDR3 having SEQ ID NO: 78; or

-a CDR1 having SEQ ID NO: 80, CDR2 having SEQ ID NO: 81, and CDR3 having SEQ ID NO: 83.

8. The antibody or functional part thereof according to any of the preceding claims, wherein the variable domain that binds an extracellular part of EGFR comprises a heavy chain variable region comprising the CDR1, CDR2 and CDR3 sequences of the variable region of MF3755 (SEQ ID NO: 89) and wherein the variable domain that binds an extracellular part of LGR5 comprises a heavy chain variable region comprising the CDR1, CDR2 and CDR3 sequences of the variable region of MF5816 (SEQ ID NO: 107).

9. The antibody or functional part thereof according to any of the preceding claims, wherein a VH chain of the variable domain that binds EGFR comprises the amino acid sequence of VH chain MF3370 (SEQ ID NO: 87); MF3755 (SEQ ID NO: 89); MF4280 (SEQ ID NO: 91) or MF4289 (SEQ ID NO: 93); or the amino acid sequence of VH chain MF3370 (SEQ ID NO: 87); MF3755 (SEQ ID NO: 89); MF4280 (SEQ ID NO: 91) or MF4289 (SEQ ID NO: 93) having at most 15, preferably not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 and preferably having not more than 5, 4, 3, 2 or 1 amino acid modifications, including insertions, deletions, substitutions or a combination thereof with respect said VH; and wherein a VH chain of the variable domain that binds LGR5 comprises the amino acid sequence of VH chain MF5790 (SEQ ID NO: 95); MF5803 (SEQ ID NO: 97); MF5805 (SEQ ID NO: 99); MF5808 (SEQ ID NO: 101); MF5809 (SEQ ID NO: 103); MF5814 (SEQ ID NO: 105); MF5816 (SEQ ID NO: 107); MF5817 (SEQ ID NO: 109); or MF5818 (SEQ ID NO: 111); or the amino acid sequence of VH chain MF5790 (SEQ ID NO: 95); MF5803 (SEQ ID NO: 97); MF5805 (SEQ ID NO: 99); MF5808 (SEQ ID NO: 101); MF5809 (SEQ ID NO: 103); MF5814 (SEQ ID NO: 105); MF5816 (SEQ ID NO: 107); MF5817 (SEQ ID NO: 109); or MF5818 (SEQ ID NO: 111) having at most 15, preferably not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 and preferably having not more than 5, 4, 3, 2 or 1 amino acid modifications, including insertions, deletions, substitutions or a combination thereof with respect said VH, wherein said modifications are not present in the CDR1, CDR2 and CDR3 regions.

10. The antibody or functional part thereof according to any of the preceding claims, wherein a VH chain of the variable domain that binds EGFR comprises the amino acid sequence of VH chain MF3370 (SEQ ID NO: 87); MF3755 (SEQ ID NO: 89); MF4280 (SEQ ID NO: 91) or MF4289 (SEQ ID NO: 93); and wherein a VH chain of the variable domain that binds LGR5 comprises the amino acid sequence of VH chain MF5790 (SEQ ID NO: 95); MF5803 (SEQ ID NO: 97); MF5805 (SEQ ID NO: 99); MF5808 (SEQ ID NO: 101); MF5809 (SEQ ID NO: 103); MF5814 (SEQ ID NO: 105); MF5816 (SEQ ID NO: 107); MF5817 (SEQ ID NO: 109); or MF5818 (SEQ ID NO: 111).

11. The antibody or functional part thereof according to any of the preceding claims, wherein a VH chain of the variable domain that binds EGFR comprises the amino acid sequence of VH chain MF3755 (SEQ ID NO: 89); or the amino acid sequence of VH chain MF3755 (SEQ ID NO: 89) having at most 15, preferably not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 and preferably having not more than 5, 4, 3, 2 or 1 amino acid modifications, including insertions, deletions, substitutions or a combination thereof with respect said VH; and wherein a VH chain of the variable domain that binds LGR5 comprises the amino acid sequence of VH chain MF5816 (SEQ ID NO: 107); or the amino acid sequence of VH chain MF5816 (SEQ ID NO: 107) having at most 15, preferably not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 and preferably having not more than 5, 4, 3, 2 or 1 amino acid modifications, including

insertions, deletions, substitutions or a combination thereof with respect said VH, wherein said modifications are not present in the CDR1, CDR2 and CDR3 regions.

12. The antibody or functional part thereof according to any of the preceding claims, wherein a VH chain of the variable domain that binds EGFR comprises the amino acid sequence of VH chain MF3755 (SEQ ID NO: 89); and wherein a VH chain of the variable domain that binds LGR5 comprises the amino acid sequence of VH chain MF5816 (SEQ ID NO: 107).

13. The antibody or functional part thereof according to any of claims 6-12 claims, wherein both variable domains comprise CDR1, CDR2 and CDR3 regions of the light chain variable region as set forth in SEQ ID NO: 113.

14. The antibody or functional part thereof according to claim 13, wherein both variable domains comprise the light chain variable region as set forth in SEQ ID NO: 113, which light chain variable region comprises from 0 to 10 amino acid insertions, deletions, substitutions, additions or a combination thereof, wherein the amino acid insertions, deletions and substitutions are not present in the CDR1, CDR2 and CDR3 light chain variable regions.

15. The antibody or functional part thereof according to claim 13, wherein CDR1 has SEQ ID NO: 118, CDR2 has SEQ ID NO: 119, and CDR3 has SEQ ID NO: 120.

16. The antibody or functional part thereof according to claim 14, wherein both variable domains comprise the light chain variable region as set forth in SEQ ID NO: 113.

17. The use according to any one of the preceding claims, wherein the topoisomerase I inhibitor is camptothecin or a derivative thereof.

18. The use according to any one of the preceding claims, wherein the topoisomerase I inhibitor is irinotecan or topotecan.

19. The use according to any one of the preceding claims, wherein the antibody is ADCC enhanced.

20. The use according to any one of the preceding claims, wherein the antibody is afucosylated.

21. An in vitro method for inhibiting proliferation of a cell that expresses EGFR and LGR5 in a system permissive for proliferation of the cell, the method comprising providing the system with a human topoisomerase I inhibitor and with an antibody or functional part thereof that comprises a variable domain that binds

an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5.

22. A pharmaceutical composition comprising an antibody or functional part thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5; and a human topoisomerase I inhibitor.

23. The pharmaceutical composition according to claim 22, wherein the antibody or functional part thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5; and a topoisomerase I inhibitor are provided in a single formulation.

24. The pharmaceutical composition according to claim 23, wherein the antibody or functional part thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5; and a topoisomerase I inhibitor are provided in separate formulations.

25. A kit comprising an antibody or functional part thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5; a human topoisomerase I inhibitor and instructions for use of the antibody and the topoisomerase I inhibitor in the treatment of any one of claims 1-19.

26. A product comprising an antibody or functional part thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5 and a human topoisomerase I inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of gastrointestinal cancer in a subject.