

Claims

1. An antibody or functional part, derivative and/or analogue thereof that comprises a variable domain that binds an extracellular part of EGFR and a
5 variable domain that binds an extracellular part of LGR5 for use in the treatment of cancer wherein the antibody or functional part, derivative and/or analogue thereof is administered with a topoisomerase I inhibitor.
2. The antibody or functional part, derivative and/or analogue thereof of claim
10 1, wherein the cancer is colorectal, pulmonary, gastrointestinal or ovarian cancer.
3. The antibody or functional part, derivative and/or analogue thereof according to any of the preceding claims, wherein the cancer is colorectal cancer.
- 15 4. The antibody or functional part, derivative and/or analogue thereof according to any of the preceding claims, wherein the antibody or functional part, derivative and/or analogue thereof and the topoisomerase I inhibitor are administered to the subject concurrently.
- 20 5. The antibody or functional part, derivative and/or analogue thereof according to any of the preceding claims, wherein the antibody or functional part, derivative and/or analogue thereof is administered to the subject prior to the topoisomerase I inhibitor.
- 25 6. The antibody or functional part, derivative and/or analogue 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 as depicted in figure 8; or the amino acid sequence of VH chain MF3755 as depicted
30 in figure 8 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 as depicted in figure 8; or
35 the amino acid sequence of VH chain MF5816 as depicted in figure 8 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.
7. The antibody or functional part, derivative and/or analogue thereof
40 according to any of the preceding claims, wherein the variable domain that binds LGR5 binds an epitope that is located within amino acid residues 21-118 of the human LGR5 sequence depicted in figure 1.

8. The antibody or functional part, derivative and/or analogue thereof according to claim 7, wherein amino acid residues at positions 43, 44, 46, 67, 90, and 91 of human LGR5 are involved in the binding of the LGR5 binding variable domain to LGR5.
- 5 9. The antibody or functional part, derivative and/or analogue thereof according to claim 7 or 8, wherein the LGR5 binding variable domain binds less to an LGR5 protein comprising one or more of the amino acid residue variations selected from 43A, 44A, 46A, 67A, 90A, and 91A.
- 10 10. The antibody or functional part, derivative and/or analogue thereof according to any of the preceding claims, wherein the variable domain that binds EGFR binds an epitope that is located within amino acid residues 420-480 of the human EGFR sequence depicted in figure 2.
- 15 11. The antibody or functional part, derivative and/or analogue thereof according to claim 10, wherein amino acid residues at positions I462, G465, K489, I491, N493 and C499 of human EGFR are involved in the binding of the EGFR binding variable domain to EGFR.
- 20 12. The antibody or functional part, derivative and/or analogue thereof according to claim 10 or 11, wherein the EGFR binding variable domain binds less to an EGFR protein comprising one or more of the amino acid residue substitutions selected from I462A, G465A, K489A, I491A, N493A and C499A.
- 25 13. The antibody or functional part, derivative and/or analogue thereof according to any of the preceding claims, wherein the topoisomerase I inhibitor is camptothecin or a derivative thereof.
- 30 14. The antibody or functional part, derivative and/or analogue thereof according to any of the preceding claims, wherein the topoisomerase I inhibitor is irinotecan or topotecan.
- 35 15. The antibody or functional part, derivative and/or analogue thereof according to any of the preceding claims, wherein the antibody is ADCC enhanced.
16. The antibody or functional part, derivative and/or analogue thereof according to any of the preceding claims, wherein the antibody is afucosylated.
- 40 17. A 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 topoisomerase I inhibitor and with an antibody or functional part, derivative and/or analogue thereof that comprises a variable

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

18. A method of treatment of cancer in a subject comprising administering
5 simultaneously or sequentially a topoisomerase I inhibitor and an antibody or functional part, derivative and/or analogue thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5 to the subject in need thereof.
19. The method of treatment of cancer according to claim 18, wherein the
10 cancer is colorectal, pulmonary, gastrointestinal or ovarian cancer.
20. The method of treatment of cancer according to claim 18, wherein the
15 cancer is colorectal cancer.
21. A pharmaceutical composition comprising an antibody or functional part,
derivative and/or analogue 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.
22. The pharmaceutical composition according to claim 21, wherein the
antibody or functional part, derivative and/or analogue 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
25 provided in a single formulation.
23. The pharmaceutical composition according to claim 22, wherein the
antibody or functional part, derivative and/or analogue thereof that comprises a
variable domain that binds an extracellular part of EGFR and a variable domain
30 that binds an extracellular part of LGR5; and a topoisomerase I inhibitor are provided in separate formulations.
24. A kit comprising an antibody or functional part, derivative and/or analogue
thereof that comprises a variable domain that binds an extracellular part of EGFR
35 and a variable domain that binds an extracellular part of LGR5; a topoisomerase I inhibitor and instructions for use of the antibody and the topoisomerase I inhibitor in the treatment of any one of claims 1-16.
25. An antibody or functional part, derivative and/or analogue thereof that
40 comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5 for use in the treatment of gastrointestinal cancer in a subject, wherein the antibody is administered simultaneously, separately or sequentially with a topoisomerase I inhibitor.

26. An antibody or functional part, derivative and/or analogue thereof that comprises a variable domain that binds an extracellular part of EGFR and a variable domain that binds an extracellular part of LGR5 for use in the manufacture of a medicament for the treatment of cancer in a subject, wherein the antibody is administered simultaneously, separately or sequentially with a topoisomerase I inhibitor.
27. An antibody or functional part, derivative and/or analogue thereof according to claim 26, for the treatment of colorectal, pulmonary, gastrointestinal or ovarian cancer.
28. An antibody or functional part, derivative and/or analogue thereof according to claim 27, for the treatment of colorectal cancer.
29. A product comprising an antibody or functional part, derivative and/or analogue 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 as a combined preparation for simultaneous, separate or sequential use in the treatment of gastrointestinal cancer in a subject.