

Claims

1. Use of 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 in the manufacture of a medicament for use in the treatment of cancer in a subject, wherein the antibody or functional part, derivative and/or analogue thereof is administered with a topoisomerase I inhibitor subject has received or is receiving a topoisomerase I inhibitor.

2. Use of a 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, 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.

3. Use of 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 in the manufacture of a medicament for the treatment of cancer in a subject.

42. The antibody or functional part, derivative and/or analogue thereof according to any one of the preceding claims claim 1, wherein the cancer is colorectal, pulmonary, gastrointestinal or ovarian cancer.

53. The antibody or functional part, derivative and/or analogue thereof according to any one of the preceding claims, wherein the cancer is colorectal cancer.

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.

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.

6. The antibody or functional part, derivative and/or analogue thereof according to any one 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 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 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~~ according to any one of the preceding claims, ~~wherein the antibody or functional part, derivative and/or analogue thereof further comprises a common light chain~~ 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 the common light chain comprises a germline IgVκ1-39 variable region V-segment ~~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.~~

9. ~~The antibody or functional part, derivative and/or analogue thereof~~ according to claim 7 or 8, wherein the light chain comprises the kappa light chain V-segment IgVκ1-39*01 ~~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. ~~The antibody or functional part, derivative and/or analogue thereof~~ according to any one of any of the preceding claims 1-6, wherein the antibody or functional part, derivative and/or analogue thereof further comprises a common light chain further comprises a light chain variable region comprising an amino acid sequence that is at least 90%, preferably at least 95%, more preferably at least 97%, more preferably at least 98%, more preferably at least 99% identical or 100% identical to the amino acid sequence of set forth in Figure 9 ~~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.~~

11. ~~The antibody or functional part, derivative and/or analogue thereof~~ according to claim 10 to any one of claims 1-6, ~~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~~ wherein the antibody or functional part, derivative and/or analogue thereof further comprises a common light chain further comprises a variable light chain having from 0 to 10, preferably

from 0 to 5 amino acid insertions, deletions, substitutions, additions or a combination thereof with respect to a sequence in Figure 9.-

12. ~~The antibody or functional part, derivative and/or analogue thereof~~use according to ~~any one of claims 1-6~~claim 10 or 11, wherein the antibody or functional part, derivative and/or analogue thereof further comprises a common light chain further comprises an LCDR1 comprising the amino acid sequence QSISSY, an LCDR2 comprising the amino acid sequence AAS, and an LCDR3 comprising the amino acid sequence QQSYSTP ~~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.~~

13. ~~The antibody or functional part, derivative and/or analogue thereof~~use according to any one of the preceding claims, wherein the topoisomerase I inhibitor is camptothecin or a derivative thereof.

14. ~~The antibody or functional part, derivative and/or analogue thereof~~use according to any one of the preceding claims, wherein the topoisomerase I inhibitor is irinotecan or topotecan.

15. ~~The antibody or functional part, derivative and/or analogue thereof~~use according to any one of the preceding claims, wherein the antibody is ADCC enhanced.

16. ~~The antibody or functional part, derivative and/or analogue thereof~~use according to any one of the preceding claims, wherein the antibody is afucosylated.

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 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 cancer is colorectal, pulmonary, gastrointestinal or ovarian cancer.~~

~~20. The method of treatment of cancer according to claim 18, wherein the cancer is colorectal cancer.~~

1821. 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.

1922. The pharmaceutical composition according to claim 1821, 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 provided in a single formulation.

203. 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 that binds an extracellular part of LGR5; and a topoisomerase I inhibitor are provided in separate formulations.

214. 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 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 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.~~

229. 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.