

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 variable domain that binds an extracellular part of LGR5 for use in the treatment of cancer in a subject, wherein said use comprises providing the
5 subject with a flat dose of 1500 mg of the antibody or functional part, derivative and/or analogue thereof.
2. An antibody or functional part, derivative and/or analogue thereof that comprises a variable domain that binds an extracellular part of EGFR and a
10 variable domain that binds an extracellular part of LGR5 for use in the treatment of gastric, esophageal, or gastro-esophageal-junction cancer in a subject.
3. An antibody or functional part, derivative and/or analogue thereof that
15 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 a gastric, esophageal, or gastro-esophageal-junction cancer in a Her2-negative subject.
- 20 4. The antibody or functional part, derivative and/or analogue thereof for use according to claim 2 or 3, wherein said use comprises providing the subject with a flat dose of 1500 mg of the antibody or functional part, derivative and/or analogue thereof.
- 25 5. The antibody or functional part, derivative and/or analogue thereof for use according to any one of the preceding claims, wherein the antibody or functional part, derivative and/or analogue thereof is provided intravenously.

6. The antibody or functional part, derivative and/or analogue thereof for use according to any one of the preceding claims, wherein the cancer has a mutation in one or more genes selected from TP53, MLH1, PIK3CA, CDKN2A, UGT1A, UGT1A8, BRAF, PTEN, and KRAS, preferably wherein the cancer
- 5 has a mutation in one or more gene selected from TP53, MLH1, CDKN2A, UGT1A, UGT1A8, BRAF, and PTEN.
7. The antibody or functional part, derivative and/or analogue thereof for use according to claim 6, wherein the cancer has one or more mutations selected
- 10 from TP53 R196T; TP53 R342T; TP53 R248Q; MLH1 V384D; PIK3CA H1047R; CDKN2A W110T; UGT1A1 G71R; UGT1A8 G71R; and KRAS G12C.
8. The antibody or functional part, derivative and/or analogue thereof for use according to any one of the preceding claims, wherein administrations of the
- 15 antibody or functional part, derivative and/or analogue thereof is weekly, biweekly or monthly.
9. The antibody or functional part, derivative and/or analogue thereof for use according to any one of the preceding claims, wherein administrations of the
- 20 antibody or functional part, derivative and/or analogue thereof is once every 2 weeks.
10. The antibody or functional part, derivative and/or analogue thereof for use according to claim 6, wherein the cancer has a mutation in the gene coding for
- 25 TP53, preferably wherein the mutation is R196T.
11. The antibody or functional part, derivative and/or analogue thereof for use according to claim 6, wherein the cancer has a mutation in the gene coding for TP53, preferably wherein the mutation is R342T, and the cancer has a

mutation in the gene coding for MLH1, preferably wherein the mutation is V384D.

12. The antibody or functional part, derivative and/or analogue thereof for use
5 according to claim 6, wherein the cancer has a mutation in the gene coding for TP53, preferably wherein the mutation is R248Q, the cancer has a mutation in the gene coding for PIK3CA, preferably wherein the mutation is H1047R, the cancer has a mutation in the gene coding for CDKN2A, preferably wherein the mutation is W110T, the cancer has a mutation in the gene coding for UGT1A1,
10 preferably wherein the mutation is G71R, and the cancer has a mutation in the gene coding for UGT1A8, preferably wherein the mutation is G71R.

13. The antibody or functional part, derivative and/or analogue thereof for use according to any one of claims 1-12, wherein the cancer is esophageal cancer,
15 preferably esophageal squamous cell carcinoma (ESCC).

14. The antibody or functional part, derivative and/or analogue thereof for use according to claim 6, wherein the cancer is a gastric cancer with a mutation in a gene selected from UGT1A1, UGT1A8, and/or PIK3CA. .
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15. The antibody or functional part, derivative and/or analogue thereof for use according to claim 6, wherein the cancer has a mutation in the gene coding for KRAS, preferably wherein the mutation is G12C, the cancer has a mutation in the gene coding for UGT1A1, preferably wherein the mutation is G71R, and
25 the cancer has a mutation in the gene coding for UGT1A8, preferably wherein the mutation is G71R.

16. The antibody or functional part, derivative and/or analogue thereof for use according to claim 2, wherein the cancer has a mutation in the gene coding for
30 UGT1A1, preferably wherein the mutation is G71R, and the cancer has a

mutation in the gene coding for UGT1A8, preferably wherein the mutation is G71R.

17. The antibody or functional part, derivative and/or analogue thereof for use
5 according to claim 10, wherein the cancer further has a mutation in PIK3CA, preferably wherein the mutation is E545K.

18. The antibody or functional part, derivative and/or analogue thereof for use
according to any one of claims 1-17, wherein the cancer is gastric cancer.
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19. The antibody or functional part, derivative and/or analogue thereof for use
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 3; or the amino acid sequence of VH chain
15 MF3755 as depicted in figure 3 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
20 chain MF5816 as depicted in figure 3; or the amino acid sequence of VH chain
MF5816 as depicted in figure 3 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.

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20. The antibody or functional part, derivative and/or analogue thereof for use
according to any one 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.

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21. The antibody or functional part, derivative and/or analogue thereof for use according to claim 20, 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.
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22. The antibody or functional part, derivative and/or analogue thereof for use according to claim 20 or 21, 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.
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23. The antibody or functional part, derivative and/or analogue thereof for use according to any one 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.
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24. The antibody or functional part, derivative and/or analogue thereof for use according to claim 23, 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.
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25. The antibody or functional part, derivative and/or analogue thereof for use according to claim 23 or 24, 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.
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26. The antibody or functional part, derivative and/or analogue thereof for use according to any one of the preceding claims, wherein the antibody is ADCC enhanced.

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

- 5 28. A method of treating gastric, esophageal, or gastro-esophageal-junction comprising administering to a subject in need thereof 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.

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29. The antibody or functional part, derivative and/or analogue thereof for use or a method according to any of the preceding claims, wherein the treatment with the antibody or functional part, derivative and/or analogue thereof is preceded by a step of diagnosing the subject for Her2 status.

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30. The antibody or functional part, derivative and/or analogue thereof according to claim 29, wherein diagnosis is by ISH or IHC testing for Her2 status.