

CLAIMS

1. An anti-Met antibody fragment comprising a single antigen binding arm and an Fc region, wherein
5 the Fc region comprises a complex of a first and a second Fc polypeptide, wherein the antibody fragment comprises:

(i) a first polypeptide comprising one humanized light chain variable (VL) domain, and one human light
10 chain constant (CL) domain, wherein the humanized VL domain is fused to the human CL domain in the N- to C-term direction, and wherein the humanized VL domain contains three complementary determining regions (CDRs) having amino acid sequences as set forth in SEQ ID No.:
15 1, 2 and 3, and wherein the humanized VL domain has an amino acid sequence as set forth in SEQ ID No.: 7;

(ii) a second polypeptide comprising one humanized heavy chain variable (VH) domain, one human heavy chain constant CH1 domain and the first Fc polypeptide,
20 wherein the first Fc polypeptide comprises one hinge region, one human constant CH2 domain and one human CH3 constant domain, wherein the humanized VH domain is fused to the human CH1 domain, that is fused to the human hinge region, that is fused to the human CH2
25 domain, that is fused to the human CH3 domain in the N- to C-term direction, and wherein the humanized VH domain contains three complementary determining regions (CDRs) having amino acid sequences as set forth in SEQ ID No.: 4, 5 and 6, and wherein the humanized VH domain
30 has an amino acid sequence as set forth in SEQ ID No.: 8; and

(iii) a third polypeptide comprising the second human Fc polypeptide, wherein the second human Fc polypeptide comprises one human hinge region, one human
35 constant CH2 domain and one human CH3 constant domain,

wherein the human hinge region is fused to the CH2 domain that is fused to the human CH3 domain in the N-to C-term direction, wherein the human hinge region is truncated at the N-terminus.

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2. The anti-Met antibody fragment according to claim 1, wherein the human CL domain is a human light kappa type domain.

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3. The anti-Met antibody fragment according to claim 1 or claim 2, wherein the human hinge region and the human constant domains CH1, CH2 and CH3 are from a human IgG1.

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4. The anti-Met antibody fragment according to any one of claims 1 to 3, wherein the two Fc polypeptides are linked through intermolecular disulfide bonds at the hinge region.

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5. The anti-Met antibody fragment according to any one of claims 1 to 4, wherein the first Fc polypeptide and the second Fc polypeptide meet at an interface, and one between the first and the second Fc polypeptide comprises a knob at the interface, and the other between the first and the second Fc polypeptide comprises a hole at the interface, wherein the knob is positionable into the hole.

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6. The anti-Met antibody fragment according to claim 5, wherein one between the first and the second Fc polypeptide comprises a mutated CH3 constant domain, wherein the mutated CH3 constant domain carries an amino acid mutation at position 389, wherein the original amino acid at position 389 has been mutated to import an amino acid having a larger side chain volume

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than the original amino acid; and wherein the other between the first and the second Fc polypeptide comprises a mutated CH3 constant domain, wherein the mutated CH3 constant domain carries three amino acid mutations at positions 389, 391 and 438, wherein the original amino acids have been mutated to import amino acids having smaller side chains volume than the original amino acids, wherein the amino acid numbering is according to the EU numbering scheme of Kabat.

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7. The anti-Met antibody fragment according to claim 6, wherein the original amino acids at positions 389, 391 and 438 are threonine, leucine and tyrosine respectively; and wherein in one between the first and the second Fc polypeptide the threonine in position 389 has been mutated to tryptophan; and wherein in the other between the first and the second Fc polypeptide the threonine at position 389 has been mutated to serine, the leucine at position 391 has been mutated to alanine and the tyrosine at position 438 has been mutated to valine.

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8. The anti-Met fragment according to any one of claims 1 to 7, wherein the human CL domain has an amino acid sequence as set forth in SEQ ID No.: 9 and the human CH1 domain has an amino acid sequence as set forth in SEQ ID No.: 10.

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9. The anti-Met antibody fragment according to any one of claims 1 to 8, wherein the first human Fc polypeptide has an amino acid sequence as set forth in SEQ ID No.: 11, and the second human Fc polypeptide has an amino acid sequence as set forth in SEQ ID No.: 12.

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10. The anti-Met antibody fragment according to

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any one of claims 1 to 9, wherein the anti-Met antibody fragment when bound to Met induces shedding of an extracellular domain of Met.

5 **11.** Isolated nucleic acid encoding the anti-Met antibody fragment of any of claims 1 to 10.

12. A composition comprising two or more recombinant nucleic acids which collectively encode the
10 anti-Met antibody fragment of any of claims 1 to 10.

13. A product comprising, in a single bottle or in two bottles, (a) an anti-Met antibody fragment according to any one of claims 1 to 10, and a
15 pharmaceutically acceptable vehicle, and (b) an extracellular portion of human Met and a pharmaceutically acceptable vehicle, wherein the extracellular portion of human Met is capable of binding to Hepatocyte Growth Factor (HGF) in a stable
20 manner and contains at least one amino acid mutation within the epitope recognized by the anti-Met antibody fragment to prevent binding of the anti-Met antibody fragment thereto.

25 **14.** The product according to claim 13, wherein the extracellular portion of human Met contains SEMA, PSI, IPT-1, IPT-2, IPT-3 and IPT-4 domains.

15. The product according to claim 13 or claim 14,
30 wherein the extracellular portion of human Met has an amino acid sequence as set forth in SEQ ID No.: 13, wherein at least one of the amino acids between position 797 and position 875 of SEQ ID No.: 13 is mutated in order to prevent binding of the anti-Met
35 antibody fragment thereto.

16. The product according to any one of claims 13 to 15, wherein the extracellular portion of human Met has an amino acid sequence as set forth in SEQ ID No.:
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17. An anti-Met antibody fragment according to any one of claims 1 to 10 or a product according to any one of claims 13 to 16 for use in the treatment of a tumor and/or metastasis in a patient carrying genetic alterations of the MET gene.
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18. A product according to any one of claims 13 to 16 for use in the treatment of a tumor and/or metastasis in a patient carrying a wild-type MET gene.
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19. Process for the manufacturing of an anti-Met antibody fragment according to any one of claims 1 to 10, the process comprising the following steps: (i) synthesis of cDNA sequences of the first, second and third polypeptides constituting the anti-Met antibody fragment, (ii) insertion of the three cDNA sequences into one or more plasmids, wherein the plasmid(s) is(are) suitable for expression in a mammalian cell line, (iii) transient or stable co-transfection of a mammalian cell line with the plasmid(s), (iv) collection of the culture supernatant, (v) purification by affinity chromatography of the anti-Met antibody fragment.
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