armed antibody fragment comprising a full length antibody heavy chain, a full length antibody light chain, and an antibody heavy chain Fc-region polypeptide, whereby the full length antibody heavy chain and the full length antibody light chain are cognate antibody chains complementary to each other and the pair of variable domains (VH and VL) thereof forms an antigen binding site that specifically binds to the second surface marker or its ligand, whereby the full length antibody heavy chain and the antibody heavy chain Fc-region polypeptide are covalently linked to each other via one or more disulfide bonds forming an antibody hinge region, and whereby the antibody heavy chain Fc-region polypeptide has an oligoglycine G_m (m = 2, or 3, or 4, or 5) amino acid sequence at its N-terminus, and (c) a nucleic acid encoding a soluble sortase A with a C-terminal endoplasmic reticulum retention signal,

and thereby producing the bispecific antibody.

In another aspect, there is provided a method for ~~selecting~~ producing a bispecific antibody comprising the following steps

(i) determining the cell surface makers present in a cell containing sample and selecting thereof at least a first surface marker and a second surface marker,

(ii) transfecting a cell with (a) a nucleic acid encoding an antibody Fab fragment, or an antibody scFab, or a scFv antibody comprising within the 20 C-terminal amino acid residues the amino acid sequence LPXTG (SEQ ID NO: 01, wherein X can be any amino acid residue) followed by an endoplasmic reticulum retention signal KDEL (SEQ ID NO: 02), whereby the Fab fragment or scFv antibody specifically binds to the first surface marker or its ligand, (b) a nucleic acid encoding an one-armed antibody fragment comprising a full length antibody heavy chain, a full length antibody light chain, and an antibody heavy chain Fc-region polypeptide, whereby the full length antibody heavy chain and the full length antibody light chain are cognate antibody chains complementary to each other and the pair of variable domains (VH and VL) thereof forms an antigen binding site that specifically binds to the second surface marker or its ligand, whereby the full length antibody heavy chain and the antibody heavy chain Fc-region polypeptide are covalently linked to each other via one or more disulfide bonds forming an antibody hinge

(ii) choosing the bispecific antibody with the suitable characteristic selected from the group consisting of binding specificity, selectivity, affinity, effector function, in vivo half-life and combinations thereof, and thereby determining a combination of antigen binding sites.

The sortase A may be the sortase A of Staphylococcus aureus (S. aureus). In one embodiment the nucleic acid encoding a (soluble) sortase A with a C-terminal endoplasmic reticulum retention signal encodes an amino acid sequence of SEQ ID NO: 51 or SEQ ID NO: 52.

~~In another aspect, t~~There is provided a bispecific antibody obtained by a method as reported herein.

~~In another aspect, t~~There is provided a bispecific antibody comprising the amino acid sequence LPXTG (SEQ ID NO: 01, wherein X can be any amino acid residue) in one of its heavy chains.

The following embodiments as reported herein are given.

In one embodiment the members of the multitude of multispecific binders are each obtained by a method as reported herein.

In one embodiment a multispecific binder is selected based on its binding specificity and/or selectivity and/or affinity and/or effector function and/or in vivo half-life.

In one embodiment the binding entity is a cognate pair of an antibody heavy chain variable domain and an antibody light chain variable domain.

In one embodiment the multispecific binder is a bispecific antibody comprising two or four binding entities.

In one embodiment the first polypeptide domain and the second polypeptide domain are selected independently of each other from full length antibody, scFv, scFab, antibody heavy chain, antibody light chain, antibody heavy chain Fc-region fragment, pair of antibody light chain variable domain and antibody heavy chain

In one embodiment the first polypeptide domain comprises i) the amino acid sequence LPXTG (SEQ ID NO: 01, wherein X can be any amino acid residue) in its C-terminal amino acid sequence region (i.e. within the twenty C-terminal amino acid residues) and ii) the endoplasmic reticulum retention signal KDEL (SEQ ID NO: 02) at its C-terminus, and the second polypeptide domain comprises an oligoglycine G_m (m = 2, or 3, or 4, or 5) at its N-terminus.

In one embodiment the second polypeptide domain or the second binding entity comprises an oligoglycine G_m (m = 2, or 3, or 4, or 5) amino acid sequence at its N-terminus.

The present disclosure may relate to a pharmaceutical formulation comprising a multispecific binder as reported herein.

The present disclosure may relate to use of a multispecific binder as reported herein in the manufacture of a medicament.

In one embodiment the medicament is for the treatment of cancer.

The present disclosure may relate to a method of treating an individual having cancer comprising administering to the individual an effective amount of a multispecific binder as reported herein.

The present disclosure may relate to a method for destroying cancer cells in an individual comprising administering to the individual an effective amount of a multispecific binder as reported herein.

~~In another aspect, t~~There is provided a pharmaceutical formulation comprising a bispecific antibody as reported herein.

~~In another aspect, t~~There is provided use of a bispecific antibody as reported herein in the manufacture of a medicament.

In one embodiment the medicament is for the treatment of cancer.

The present disclosure may relate to a method of treating an individual having cancer comprising administering to the individual an effective amount of a bispecific antibody as reported herein.

The present disclosure may relate to a method for destroying cancer cells in an individual comprising administering to the individual an effective amount of a

6. The method according to any one of claims 1 to 5, characterized in that the endoplasmic reticulum retention signal is selected from SEQ ID NO: 02 (KDEL), SEQ ID NO: 03 (HDEL), or SEQ ID NO: 04 (SFIXXXXMP).

7. The method according to any one of claims 1 to 6, characterized in that the sortase motif is LPXTG (SEQ ID NO: 01, wherein X can be any amino acid residue).

8. The method according to any one of claims 1 to 7, characterized in that the first binding domain or the first binding entity has within the 20 C-terminal amino acid residues the amino acid sequence LPXTG (SEQ ID NO: 01, wherein X can be any amino acid residue).

9. A method for ~~selecting~~ producing a bispecific antibody comprising the following steps

(i) determining the cell surface makers present in a cell containing sample and selecting thereof at least a first surface marker and a second surface marker,

(ii) transfecting a cell with (a) a nucleic acid encoding an antibody Fab fragment, or an antibody scFab, or a scFv antibody comprising within the 20 C-terminal amino acid residues the amino acid sequence LPXTG (SEQ ID NO: 01, wherein X can be any amino acid residue) followed by an endoplasmic reticulum retention signal KDEL (SEQ ID NO: 02), whereby the Fab fragment or scFv antibody specifically binds to the first surface marker or its ligand, (b) a nucleic acid encoding an one-armed antibody fragment comprising a full length antibody heavy chain, a full length antibody light chain, and an antibody heavy chain Fc-region polypeptide, whereby the full length antibody heavy chain and the full length antibody light chain are cognate antibody chains complementary to each other and the pair of variable domains (VH and VL) thereof forms an antigen binding site that specifically binds to the second surface marker or its ligand, whereby the full length antibody heavy chain and

(ii) choosing the bispecific antibody with the suitable characteristic selected from the group consisting of binding specificity, selectivity, affinity, effector function, in vivo half-life and combinations thereof, and thereby determining a combination of antigen binding sites.

~~11. A bispecific antibody comprising the amino acid sequence LPXTG (SEQ ID NO: 01, wherein X can be any amino acid residue) in one of its heavy chains.~~

~~12~~11. The method according to any one of claims 5 to 9 ~~or the antibody according to any one of claims 15 or 16~~, characterized in that Fc-region comprises a mutation of the naturally occurring amino acid residue at position 329 and at least one further mutation of at least one amino acid residue selected from the group comprising amino acid residues at position 228, 233, 234, 235, 236, 237, 297, 318, 320, 322 and 331 to a different residue, wherein the residues in the Fc-region are numbered according to the EU index of Kabat.