

have a too limited specificity, e.g. 1.23A mAb only recognizes the human SIRP α polymorphic variant SIRP α_1 and not the variant SIRP α_{BIT} , which is predominant in at least the Caucasian population (X.W. Zhao *et al. PNAS* 2011, 108(45), 18342-18347).

Besides using anti-SIRP α antibodies to increase ADCC of a therapeutic antibody, these antibodies may also be used to directly target SIRP α -expressing cancer types. Anti-SIRP α antibodies comprising wild-type human -Fc may be suitable to treat cancers expressing SIRP α , such as renal cell carcinoma and malignant melanoma, as murine anti-SIRP α antibodies having a functional Fc region slowed tumour formation in mice injected with Renca cells and B16BL6 melanoma cells, both expressing SIRP α (Yanagita *et al. JCI Insight* 2017, 2(1), e89140).

In conclusion, a need remains for anti-SIRP α antibodies which have low binding to SIRP γ , which bind specifically to both SIRP α_1 and SIRP α_{BIT} polymorphic variants and which are suitable for use in anti-cancer therapy either alone or in combination with therapeutic antibodies.

BRIEF DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to antibodies against SIRP α that are suitable for use in anti-cancer therapy. The invention further relates to the use of the antibodies in the treatment of human solid tumours and haematological malignancies.

SUMMARY

In one aspect, the present disclosure refers to an anti-SIRP α antibody or an antigen-binding fragment thereof, comprising heavy chain (HC) and light chain (LC) variable region (VR) complementarity determining regions (CDRs), wherein: (i) HC CDRs 1, 2 and 3 are the CDRs of HC VR amino acid sequence SEQ ID NO:13; and (ii) LC CDRs 1, 2 and 3 are the

CDRs of LC VR amino acid sequence SEQ ID NO:14; wherein the CDRs are determined according to Kabat numbering.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising the anti-SIRP α antibody or antigen-binding fragment thereof as disclosed herein and one or more pharmaceutically acceptable excipients.

In another aspect, the present disclosure refers to a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating human solid tumours or haematological malignancies.

In yet another aspect, the present disclosure refers to a use of a combination of the anti-SIRP α antibody or antigen-binding fragment thereof as disclosed herein or the pharmaceutical composition as disclosed herein with one or more other anti-cancer therapeutics in the manufacture of a medicament for treating human solid tumours or haematological malignancies.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Comparison of the ADCC measured in % cytotoxicity of trastuzumab (Tmab) alone, trastuzumab in combination with the murine 12C4 anti-SIRP α antibody (mu12C4), trastuzumab in combination with an antibody wherein murine 12C4 variable regions are grafted onto the human IgG₁ constant region (12C4huIgG₁), and trastuzumab in combination

CLAIMS

1. An anti-SIRP α antibody or an antigen-binding fragment thereof, comprising
heavy chain (HC) and light chain (LC) variable region (VR) complementarity
5 determining regions (CDRs), wherein:
 - (i) HC CDRs 1, 2 and 3 are the CDRs of HC VR amino acid sequence SEQ ID
NO:13; and
 - (ii) LC CDRs 1, 2 and 3 are the CDRs of LC VR amino acid sequence SEQ ID
NO:14;
- 10 wherein the CDRs are determined according to Kabat numbering.
2. The anti-SIRP α antibody or antigen-binding fragment thereof according to claim
1, which is chimeric, humanized or human.
3. The anti-SIRP α antibody or antigen-binding fragment thereof according to claim
2, which is humanized.
- 15 4. The anti-SIRP α antibody or antigen-binding fragment thereof according to claim
3, comprising
 - a. HCVR amino acid sequence of SEQ ID NO:35 and LCVR amino acid
sequence of SEQ ID NO:36;

- b. HCVR amino acid sequence of SEQ ID NO:35 and LCVR amino acid sequence of SEQ ID NO:37;
- c. HCVR amino acid sequence of SEQ ID NO:13 and LCVR amino acid sequence of SEQ ID NO:38; or
- 5 d. HCVR amino acid sequence of SEQ ID NO:13 and LCVR amino acid sequence of SEQ ID NO:37.
5. The anti-SIRP α antibody or antigen-binding fragment thereof according to any one of claims 1 to 4, comprising a modified Fc region that exhibits reduced binding to a human Fc α or Fc γ receptor compared to the same anti-SIRP α
- 10 antibody comprising a wild-type Fc region.
6. The anti-SIRP α antibody or antigen-binding fragment thereof according to claim 5, comprising a modified human IgG₁ Fc region comprising amino acid substitutions at one or more positions selected from the group consisting of L234, L235, G237, D265, D270, N297, A327, P328, and P329 according to Eu
- 15 numbering.
7. The anti-SIRP α antibody or antigen-binding fragment thereof according to claim 6, comprising the amino acid substitutions L234A and L235A; L234E and L235A; L234A, L235A and P329A; or L234A, L235A and P329G.

8. The anti-SIRP α antibody or antigen-binding fragment thereof according to claim 7, comprising the amino acid substitutions L234A and L235A; or L234E and L235A.
9. A pharmaceutical composition comprising the anti-SIRP α antibody or
5 antigen-binding fragment thereof according to any one of claims 1 to 8 and one or more pharmaceutically acceptable excipients.
10. The pharmaceutical composition according to claim 9 for use as a medicament.
11. Use of a pharmaceutical composition according to claim 9 in the manufacture of a medicament for treating human solid tumours or haematological malignancies.
- 10 12. Use of a combination of the anti-SIRP α antibody or antigen-binding fragment thereof according to any one of claims 1 to 8 or the pharmaceutical composition according to claim 9 with one or more other anti-cancer therapeutics in the manufacture of a medicament for treating human solid tumours or haematological malignancies.
- 15 13. The use according to claim 12, wherein the one or more other anti-cancer therapeutics are targeted therapeutics or immunotherapeutic agents.
14. The use according to claim 13, wherein the targeted therapeutic is a therapeutic antibody or an antibody-drug conjugate.

15. The use according to claim 14, wherein the therapeutic antibody is a therapeutic antibody against a membrane-bound target on the surface of tumour cells which comprises a human Fc region that binds to activating Fc receptors present on human immune effector cells.