another indication that finding an antibody with sufficient specificity, in antagonistic over agonistic effects, on c-Met, as well as an acceptable therapeutic window is far from straightforward.

Nevertheless, in view of the critical role in cancer progression, c-Met remains an attractive target and the need for therapeutic antibodies and ADCs that have the desired selectivity, specificity and efficacy, as well as an acceptable therapeutic window remains.

SUMMARY

The present disclosure relates to antibodies or antigen-binding fragments thereof that specifically bind to c-Met, as well as to antibody-drug conjugates (ADCs) comprising these anti-c-Met antibodies or antigen-binding fragments.

In a first aspect, the present disclosure relates to an antibody or an antigen-binding fragment thereof that specifically binds to c-Met, comprising heavy chain (HC) variable region complementarity determining regions (CDRs) HC CDRs 1-3, wherein

the amino acid sequence of HC CDR1 comprises SEQ ID NO:26;

the amino acid sequence of HC CDR2 comprises SEQ ID NO:27; and

the amino acid sequence of HC CDR3 comprises SEQ ID NO:28;

and light chain (LC) variable region complementarity determining regions (CDRs) LC CDRs 1-3, wherein

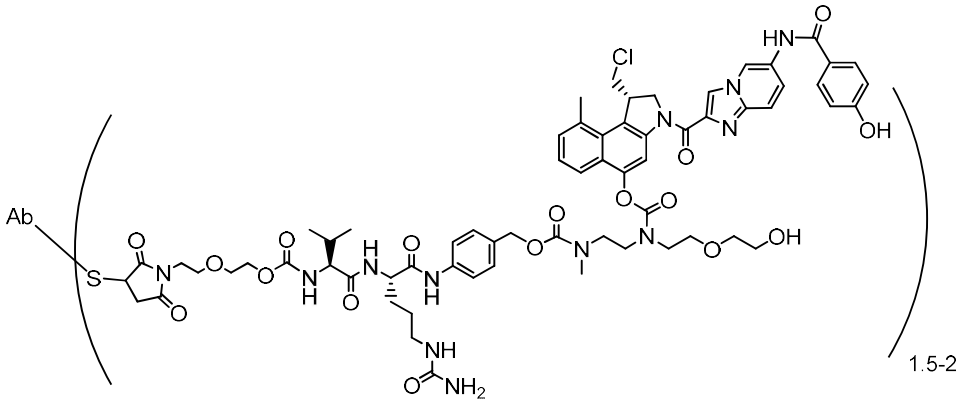
the amino acid sequence of LC CDRl comprises SEQ ID NO:29;

the amino acid sequence of LC CDR2 comprises SEQ ID NO:30; and

the amino acid sequence of LC CDR3 comprises SEQ ID NO:31.

In a second aspect, the present disclosure relates to an ADC comprising the anti-c-Met antibody or antigen-binding fragment conjugated to a cytotoxic drug through a linker.

In a preferred example, the ADC is of formula (III)



(III),

wherein

the HC variable region of Ab is represented by the amino acid sequence of SEQ ID NO:16 and the LC variable region of Ab is represented by the amino acid sequence of SEQ ID NO:20;

Ab is an IgG1 antibody; and wherein

the cytotoxic drug is site-specifically conjugated through the linker to an engineered cysteine on HC position 41 (according to Kabat numbering). In one aspect, the present invention refers to a use of an antibody or antigen-binding fragment as disclosed herein, an antibody-drug conjugate as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a c-Met positive human solid tumor or *MET*-driven hematological malignancy. In another aspect, the present invention refers to a use of a combination of an antibody or antigen-binding fragment as disclosed herein, an antibody-drug as disclosed herein or a pharmaceutical composition as disclosed herein with a therapeutic antibody, a chemotherapeutic agent and/or an antibody-drug conjugate against a cancer-related target other than the c-Met antigen in the manufacture of a medicament for the treatment of a c-Met positive human solid tumor.

Other aspects of the present disclosure include a pharmaceutical composition comprising the antibody, antigen-binding fragment or ADC and its use as a medicament, particularly for the treatment of cancer, either in mono- or in combination therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Quantification of internalization kinetics of Alexa Fluor 488 (AF488) labelled mAb3b in c-Met-positive MKN45 cells. (A) Internalization determined on the IncuCyte S3 instrument by monitoring the increase of fluorescent signal internalized in the cytoplasm followed for 24 hours. (B) Percentage internalization measured by flow cytometry.

Figure 2. Cellular binding of ADC3b and its corresponding unconjugated antibody mAb3b on c-Met positive MKN45 cells.

Figure 3. *In vitro* cytotoxicity of ADC3b in human tumor cell lines with varying levels of c-Met expression.

Figure 4. Bystander cytotoxicity in c-Met-negative Jurkat NucLight Red cells 1:1 co-cultured with c-Met positive MKN45 cells and treated with 1 µg/mL ADC3b or non-binding control ADC.

Figure 5. *In vivo* efficacy of chimeric ADCs ADC1, ADC2 and ADC3, and vehicle in a c-Met positive MKN-45 tumor model in female ces1c KO mice.

Figure 6. *In vivo* efficacy of humanized ADCs and vehicle in a c-Met positive MKN-45 tumor model in female ces1c KO mice.

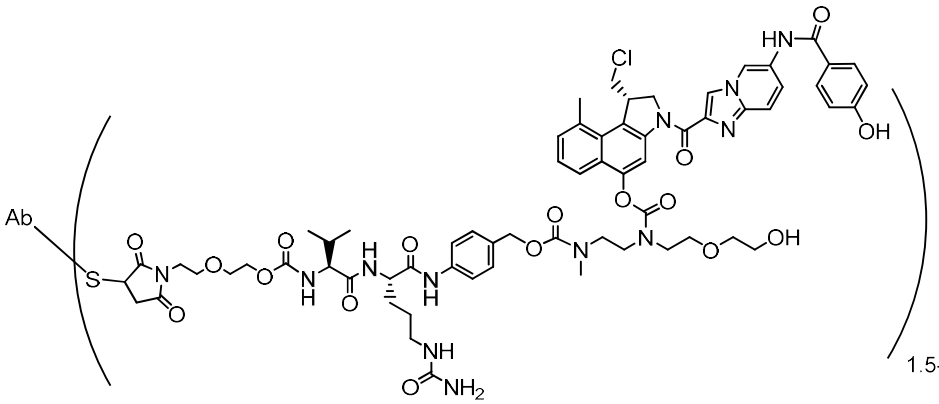
Figure 7. *In vivo* efficacy of humanized ADCs ADC3a, ADC3b and ADC3c, and vehicle in a c-Met positive MKN-45 tumor model in female ces1c KO mice.

Figure 8. Efficacy of ADC3b in the non-*MET* amplified head and neck cancer PDX model HNXF1905 (A) and lung cancer PDX model LXFL1176 (B). The arrow indicates the moment of randomization and dosing of the mice.

CLAIMS

1. An antibody or an antigen-binding fragment thereof that specifically binds to the mesenchymal-epithelial transition factor (c-Met), comprising heavy chain (HC) variable region complementarity determining regions (CDRs) HC CDRs 1-3, wherein
the amino acid sequence of HC CDR1 comprises SEQ ID NO:26;
the amino acid sequence of HC CDR2 comprises SEQ ID NO:27; and
the amino acid sequence of HC CDR3 comprises SEQ ID NO:28;
and light chain (LC) variable region complementarity determining regions (CDRs) LC CDRs 1-3, wherein
the amino acid sequence of LC CDRl comprises SEQ ID NO:29;
the amino acid sequence of LC CDR2 comprises SEQ ID NO:30; and
the amino acid sequence of LC CDR3 comprises SEQ ID NO:31.
2. An antibody or an antigen-binding fragment thereof according to claim 1, which is a humanized antibody or antigen-binding fragment.
3. An antibody or an antigen-binding fragment thereof according to claim 1 or 2, wherein the amino acid sequence of the HC variable region is represented by SEQ ID NO:16 and the amino acid sequence of the LC variable region is represented by SEQ ID NO:20.
4. An antibody according to any one of claims 1-3, which is an intact IgG1 antibody.
5. An antigen-binding fragment according to any one of claims 1-3, which is a Fab fragment.
6. An antibody-drug conjugate comprising the antibody or antigen-binding fragment according to any one of claims 1-5 conjugated to a cytotoxic drug through a linker, preferably through a cleavable linker.
7. An antibody-drug conjugate according to claim 6, wherein the cytotoxic drug is a duocarmycin derivative.

8. An antibody-drug conjugate according to claim 6 or 7 of formula (III)



(III),

wherein

Ab is an IgG1 antibody;

the HC variable region of Ab is represented by the amino acid sequence of SEQ ID NO:16 and the LC variable region of Ab is represented by the amino acid sequence of SEQ ID NO:20; and

the cytotoxic drug is site-specifically conjugated through the linker to an engineered cysteine on HC position 41 according to Kabat numbering.

9. A pharmaceutical composition comprising an antibody or antigen-binding fragment according to any one of claims 1-5 or an antibody-drug conjugate according to any one of claims 6-8 and one or more pharmaceutically acceptable excipients, preferably in the form of a lyophilized powder.

10. An antibody or antigen-binding fragment according to any one of claims 1-5, an antibody-drug conjugate according to any one of claims 6-8 or a pharmaceutical composition according to claim 9 for use as a medicament.

11. Use of an antibody or antigen-binding fragment according to any one of claims 1-5, an antibody-drug conjugate according to any one of claims 6-8, or a pharmaceutical composition according to claim 9, in the manufacture of a medicament for the treatment of a c-Met positive human solid tumor or *MET*-driven hematological malignancy.

12. The use according to claim 11, wherein the c-Met positive human solid tumor is selected from the group consisting of breast cancer; brain cancer; head and neck cancer; thyroid cancer; salivary gland cancer; soft tissue sarcoma; ocular cancer; esophageal cancer; gastric cancer; small intestine cancer; colorectal cancer; urothelial cell cancer; ovarian cancer; uterine cancer; endometrial cancer; cervical cancer; lung cancer (especially non-small cell lung cancer and small-cell lung cancer); melanoma; liver

cancer; pancreatic cancer; non-melanoma skin cancer; prostate cancer; germ cell cancer; and cancer of unknown primary.

13. The use according to claim 11, wherein the *MET*-driven hematological malignancy is a lymphoid malignancy, preferably a mature T and NK neoplasm.

14. Use of a combination of an antibody or antigen-binding fragment according to any one of claims 1-5, an antibody-drug conjugate according to any one of claims 6-8 or a pharmaceutical composition according to claim 9 with a therapeutic antibody, a chemotherapeutic agent and/or an antibody-drug conjugate against a cancer-related target other than the c-Met antigen in the manufacture of a medicament for the treatment of a c-Met positive human solid tumor.