

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2023/029676

International filing date (day/month/year)
08.08.2023

Priority date (day/month/year)
10.08.2022

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/30 C07K16/28 A61K39/00

Applicant
MERCK SHARP & DOHME LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Klee, Barbara

Telephone No. -0



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement
- | | | |
|-------------------------------|-------------|-------------|
| Novelty (N) | Yes: Claims | <u>1-91</u> |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | <u>1-91</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-91</u> |
| | No: Claims | |
2. Citations and explanations
- see separate sheet**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2023/029676

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

Reference is made to the following documents:

- D1 WO 2018/157147 A1 (DRAGONFLY THERAPEUTICS INC [US]) 30 August 2018 (2018-08-30)
- D2 WO 2022/031965 A1 (DRAGONFLY THERAPEUTICS INC [US]) 10 February 2022 (2022-02-10)
- D3 EP 3 981 793 A1 (BIOTHEUS INC [CN]) 13 April 2022 (2022-04-13)

1 Summary of the documents cited:

D1 discloses multi-specific binding proteins that bind the **NKG2D receptor**, **CD16**, and a tumor-associated antigen selected from carbonic anhydrase 9 (CAIX), anoctamin-1 (ANO1), mesothelin, TROP2, **CEA** and claudin-18.2 are described, as well as pharmaceutical compositions and therapeutic methods useful for the treatment of cancer.

D2 discloses a protein comprising:

- (a) a first polypeptide comprising the amino acid sequence of SEQ ID NO: 167 (A49MI-VH-CH1-Fc; anti-NKG2D antibody VH A49MI heavy; chain 100% identical and similar to SEQ ID NO: 549)
- (b) a second polypeptide comprising the amino acid sequence of SEQ ID NO: 164 (100% identical and similar to SEQ ID NO: 550; anti-NKG2D antibody VH A49MI light chain); and
- (c) a third polypeptide comprising the amino acid sequence of SEQ ID NO: 165.

D3 discloses a monoclonal antibody and antigen-binding fragment thereof which can specifically bind to human carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5); also disclosed is a chimeric antigen receptor based on said antibody, and a method for preparing said antibody and antigen-binding fragment and use thereof for treating CEACAM5-related tumors.

2 The application lacks unity.

2.1 The following groups of potential inventions are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT:

Group I claims 1-91:

1. A protein comprising:

- (a) a first antigen-binding site that binds NKG2D;
- (b) a second antigen-binding site that binds CEACAM5; and
- (c) a third antigen-binding site, or an antibody Fc domain or a portion thereof, that binds CD 16, wherein:

the second antigen-binding site that binds CEACAM5 comprises a heavy-chain variable domain (VH) comprising a complementarity-determining region (CDR) 1 (CDRH1), CDRH2, and CDRH3, and a light-chain variable domain (VL) comprising a CDR 1 (CDL1), CDRL2, and CDRL3, wherein:

- (a) the CDRH1, CDRH2, and CDRH3 of the second antigen-binding site are:
 - (i) SEQ ID NOs: 3, 37, and 38, respectively; and
- b) the CDRL1, CDRL2, and CDRL3 of the second antigen-binding site are:
 - (i) SEQ ID NOs: 7, 8, and 9, respectively:

OR

2. A protein comprising:

- (a) a first polypeptide comprising the amino acid sequence of SEQ ID NO:549;
- (b) a second polypeptide comprising the amino acid sequence of SEQ ID NO: 550; and
- (c) a third polypeptide comprising an amino acid sequence selected from the group consisting of: SEQ ID NOs:702.

3. OR: A protein comprising an antigen-binding site that binds CEACAM5, wherein the antigen-binding site comprises a heavy-chain variable domain (VH) comprising a complementarity-determining region (CDR) 1 (CDRH1), CDRH2, and CDRH3, and a light-chain variable domain (VL) comprising a CDR 1 (CDL1), CDRL2, and CDRL3, wherein:

- (a) the CDRH1, CDRH2, and CDRH3 of the second antigen-binding site are:
 - (i) SEQ ID NOs: 3, 37, and 38, respectively; and
- b) the CDRL1, CDRL2, and CDRL3 of the second antigen-binding site are:
 - (i) SEQ ID NOs: 7, 8, and 9.

Group II claims 1-91:

1. A protein comprising:

- (a) a first antigen-binding site that binds NKG2D;
- (b) a second antigen-binding site that binds CEACAM5; and
- (c) a third antigen-binding site, or an antibody Fc domain or a portion thereof, that binds CD 16, wherein:
the second antigen-binding site that binds CEACAM5 comprises a heavy-chain variable domain (VH) comprising a complementarity-determining region (CDR) 1 (CDRH1), CDRH2, and CDRH3, and a light-chain variable domain (VL) comprising a CDR 1 (CDL1), CDRL2, and CDRL3, wherein:
 - (a) the CDRH1, CDRH2, and CDRH3 of the second antigen-binding site are:
 - (i) SEQ ID NOs: 3, 718, and 6, respectively; and
 - (b) the CDRL1, CDRL2, and CDRL3 of the second antigen-binding site are:
 - (i) SEQ ID NOs: 40, 41, and 42;

2. OR: A protein comprising:

- (a) a first polypeptide comprising the amino acid sequence of SEQ ID NO:549;
- (b) a second polypeptide comprising the amino acid sequence of SEQ ID NO: 550; and
- (c) a third polypeptide comprising an amino acid sequence selected from the group consisting of: SEQ ID NOs: 706,

3. OR: A protein comprising an antigen-binding site that binds CEACAM5, wherein the antigen-binding site comprises a heavy-chain variable domain (VH) comprising a complementarity-determining region (CDR) 1 (CDRH1), CDRH2, and CDRH3, and a light-chain variable domain (VL) comprising a CDR 1 (CDL1), CDRL2, and CDRL3, wherein:

- (a) the CDRH1, CDRH2, and CDRH3 of the second antigen-binding site are:
 - (i) SEQ ID NOs: 3, 718, and 6, respectively; and
- b) the CDRL1, CDRL2, and CDRL3 of the second antigen-binding site are:
 - (i) SEQ ID NOs: 40, 41, and 42.

Group III claims 1-91:

1. A protein comprising:

- (a) a first antigen-binding site that binds NKG2D;
- (b) a second antigen-binding site that binds CEACAM5; and
- (c) a third antigen-binding site, or an antibody Fc domain or a portion thereof, that binds CD 16, wherein:

the second antigen-binding site that binds CEACAM5 comprises a heavy-chain variable domain (VH) comprising a complementarity-determining region (CDR) 1 (CDRH1), CDRH2, and CDRH3, and a light-chain variable domain (VL) comprising a CDR 1 (CDL1), CDRL2, and CDRL3, wherein:

- (a) the CDRH1, CDRH2, and CDRH3 of the second antigen-binding site are:
 - (iii) SEQ ID NOs: 102, 104, and 105 and
- (b) the CDRL1, CDRL2, and CDRL3 of the second antigen-binding site are:
 - (iii) SEQ ID NOs: 107, 108, and 109.

2. OR: A protein comprising:

- (a) a first polypeptide comprising the amino acid sequence of SEQ ID NO:549;
- (b) a second polypeptide comprising the amino acid sequence of SEQ ID NO: 550; and
- (c) a third polypeptide comprising an amino acid sequence selected from the group consisting of: SEQ ID NOs: 709 or 713.

3. OR: A protein comprising an antigen-binding site that binds CEACAM5, wherein the antigen-binding site comprises a heavy-chain variable domain (VH) comprising a complementarity-determining region (CDR) 1 (CDRH1), CDRH2, and CDRH3, and a light-chain variable domain (VL) comprising a CDR 1 (CDL1), CDRL2, and CDRL3, wherein:

- (a) the CDRH1, CDRH2, and CDRH3 of the second antigen-binding site are:
 - (i) SEQ ID NOs: 102, 104, and 105; and
- (b) the CDRL1, CDRL2, and CDRL3 of the second antigen-binding site are:
 - (i) SEQ ID NOs:107, 108 and 109.

2.2 The reasons are as follows:

The common matter linking these groups (I-III) of potential inventions (**item 1.**) is the provision of a protein comprising:

- (a) a first antigen-binding site that binds NKG2D;
- (b) a second antigen-binding site that binds CEACAM5; and
- (c) a third antigen-binding site, or an antibody Fc domain or a portion thereof, that binds CD 16.

The feature of the exact sequence of the 6 CDRs or the CVH of the second antigen-binding site that binds CEACAM5 of potential invention I-III respectively are not identical but share the same technical effect of binding to

- (b) a second antigen-binding site that binds CEACAM5; and

and solve the problem to provide a protein binding to NKG2D, CEACAM5 and CD16. This means these features are corresponding and therefore also form part of the common matter.

This common matter is already known because D1 (claims 1-34, 41-52) provides a protein binding to NKG2D, CEACAM5 and CD16.

The common matter therefore cannot constitute a single general inventive concept linking the alternatives within independent claim 1 and claims 2-34.

The exact sequences of the 6 CDRs of the second binding moiety to CEACAM5 of inventions I to III differs from the common matter.

The second binding moieties to CEACAM5 do not share any structural similarity. Without such a shared structural element linked to a common property or activity, no same or corresponding special technical features can be identified.

The problem to be solved by the present invention may therefore be regarded as the provision of another second antigen binding site that binds CEACAM5.

Each of the potential inventions solves the same objective technical problem of providing alternative a protein binding to NKG2D, CEACAM5 and CD16.

D1 already discloses a protein binding to NKG2D, CEACAM5 and CD16.

Since this objective technical problem is known from the prior art (see above), the provision of further compounds cannot be considered to constitute a corresponding special technical feature making a contribution over the prior art.

As the claims do not comprise the same or corresponding special technical features, they lack the technical relationship between their subject-matter and the claims are not so linked as to form a single general inventive concept.

The application therefore does not fulfil the requirement for unity of invention.

With respect to groups I-III (item 2.) it is noted that only binding of a protein to a first and second binding site each binding NKG2D and the third antigen-binding site that binds CEACAM5 is required. No binding to CD16 is required.

D2 discloses a protein binding to (a) a polypeptide comprising SEQ ID NO: 549 (A49MI-VH-CH1Fc; SEQ ID NO: 166) and a polypeptide comprising the amino acid sequence SEQ ID NO: 550 (A49MI-VL-CL, SEQ ID NO: 164) both binding to NKG2D , and a binding site that binds EGFR (SEQ ID NO: 165)

D2 does not disclose SEQ ID NOs: 702, 706, 709 or 713.

With respect to groups I-III (**item 3**) it is noted that only the binding site binding to CEACAM5 is claimed. D1 (claims 1-61) or D2 (claim 66, SEQ ID NOs: 174, 165) or D3 (claims 1-25) disclose binding sites that bind CEACAM5.

Thus the same rationale applies with respect to lack of unity regarding items 2 and 3:

This common matter is already known because D1 (claims 1-61) or D2 (claim 66, SEQ ID NOs: 174, 165) provide a protein binding to CEACAM5 and CD16. Moreover D1 or D2 or D3 provide a protein binding to CEACAM5.

The common matter therefore cannot constitute a single general inventive concept linking the alternatives within independent claim 35, claim 53 and claims dependent thereon.

The exact sequences of the 6 CDRs of the binding moiety to CEACAM5 of inventions I to III differs from the common matter.

The binding moieties to CEACAM5 do not share any structural similarity. Without such a shared structural element linked to a common property or activity, no same or corresponding special technical features can be identified.

The problem to be solved by the present invention may therefore be regarded as the provision of another antigen binding site that binds CEACAM5.

Since this objective technical problem is known from the prior art (see above), the provision of further compounds cannot be considered to constitute a corresponding special technical feature making a contribution over the prior art.

As the claims do not comprise the same or corresponding special technical features, they lack the technical relationship between their subject-matter and the claims are not so linked as to form a single general inventive concept.

The application therefore does not fulfil the requirement for unity of invention.

All three inventions have been searched.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3 *Industrial applicability (Art. 33(4) PCT)*

Claims 1-91 meet the requirements for industrial applicability according to Art. 33(4) PCT.

4 *Rule 39.1 (iv) / 67.1 (iv) PCT*

Claims 44-52, 84-91, relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1 (iv) / 67.1 (iv) PCT:

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. Patentability, in particular novelty and inventive step, of claims 44-52, 84-91 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

In case the application enter the European Regional Phase, the applicant is informed that

- 1) claims in the format "Substance/composition X for use in the treatment of disease Y" are considered allowable, and
- 2) a claim in the form "Use of a substance or composition X for the manufacture of a medicament for therapeutic application Z" is allowable for either a first or "subsequent" (second or further) such application ("Swiss type" claim), if this application is new and inventive and has a filing or earliest priority date before 29 January 2011 (which is presently not the case, see claims 46, 47, 86, 87, 88).

5 *Novelty (Article 33(1) PCT and Article 33(2) PCT)*

The protein comprising (a) a first antigen-binding site that binds NKG2D;
(b) a second antigen-binding site that binds CEACAM5; and
(c) a third antigen-binding site, or an antibody Fc domain or a portion thereof,

that binds CD16 of claim 1 and claims directly or indirectly dependent thereon is new because none of the document cited discloses the specific CDR sequences.

Therefore the subject matter of claims 1-34 is new in view of D1 or D2.

The same applies with respect to claim 35, because none of the documents cited discloses SEQ ID NO: 702, 706, 709, and 713.

The same applies with respect to claim 53 because none of the document cited discloses the specific CDR sequences.

6 Inventive step (Article 33(1) PCT and Article 33(3) PCT)

6.1 With respect to claim 1:

D1 is considered as the closest prior art. D1 already discloses a protein binding to NKG2D, CEACAM5 and CD16, from which the subject matter of claim 1 differs by the feature of the exact sequence of the 6 CDRs (SEQ ID NOs: 3, 37, 38, 7, 8, 9) or (SEQ ID NOs: 3, 718, 6, 40, 41, 42) or SEQ ID NOs: 102, 104, 105, 107, 108, 109) .

The technical effect associated with said difference can't be ascertained due to missing comparative results.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative protein binding to NKG2D, CEACAM5 and CD16.

The solution proposed in claim 1 of the present application cannot be considered to involve an inventive step.

The skilled person with a knowledge of D1 and motivated to provide an alternative protein binding to NKG2D, CEACAM5 and CD16 would find it obvious to produce an protein binding to NKG2D, CEACAM5 and CD16 further using routine methods and those taught in said D1 in order to solve the problem posed.

6.2 The same applies in analogy with respect to claim 35 (and claims 36-40, 42-52 directly or indirectly dependent thereon) the protein binding to CEACAM5 and CD16 in view of D1 (claims 1-61) or D2 (claim 66, SEQ ID NOs: 164, 165), and to claim 53 (and claims 54-91 directly or indirectly dependent thereon) the protein binding to CEACAM5 in view of D1 (claims 1-61) or D2 (claim 66, SEQ ID NOs: 164, 165) or D3 (claims 1-25). Thus the same applies to the respective

nucleic acid, the expression vector, the host cell, the method of producing or the medical use and to claims dependent thereon which do not appear to contain any additional features which, in combination with the features of any claim to which they refer.

Re Item VIII

Certain observations on the international application

- 7 The subject matter of claims 25, 26 , 29-32, 71-74 lacks an essential feature, since the degree of sequence variability encompassed by the claims includes the CDR regions. It is well known in the art that a change in a single amino acid in a CDR may be sufficient to abolish binding to the target. Therefore the subject matter of claims s 25, 26 , 29-32, 71-74 is not clearly defined.
- 8 It is not sufficient to characterise an antibody with only a part of a CDR sequence or a combination of CDRs out of a plurality of CDR sequences provided. An antibody is structurally made of two light and two heavy chains and it needs at least 6 specifically defined CDRs to confer antigen binding specificity. Unless the contrary is shown it is considered that a combination of CDRs out of a list is neither equivalent to an antibody, nor sufficient to define the specificity of an antibody. Since the claims do not clearly define the structure of the antibodies, they do not meet the requirement following from Article 6 PCT. Therefore the subject matter of claims 1 and 2, claims 53, 54 is not clearly defined. The same applies with respect to the claims directly or indirectly dependent thereon.
- 9 In addition it should be noted that if the surprising technical effect involves the binding affinity, the structural requirements for conventional antibodies inherently reflecting this affinity must comprise the six CDRs and the framework regions because the framework regions also can influence the affinity.
- 10 Although claims 1, 35-42, 53, 78-83 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.