

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.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/US2018/035492

International filing date (day/month/year)
31.05.2018

Priority date (day/month/year)
02.06.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61K35/17 C07K14/725

Applicant
PFIZER INC.

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 43 <i>bis</i> .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 66.1 *bis*(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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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 43*bis*.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:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>2-15, 22-31, 33, 34, 36-42, 45, 47, 49, 50, 67-87</u>
	No: Claims	<u>1, 16-21, 32, 35, 43, 44, 46, 48, 51-66</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-87</u>
Industrial applicability (IA)	Yes: Claims	<u>1-87</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Item V

V.1 Reference is made to the following documents:

- D1 WO 2017/053889 A2 (PREC IMMUNOTHERAPY INC [US]) 30 March 2017 (2017-03-30)
- D2 CHRISTOPHER DANIEL CHIEN ET AL: "Preclinical Development of FLT3-Redirected Chimeric Antigen Receptor T Cell Immunotherapy for Acute Myeloid Leukemia", BLOOD, vol. 128, no. 22 2 December 2016 (2016-12-02), page 1, XP002779137
- D3 WO 2009/155015 A1 (IMCLONE LLC [US]; LI YIWEN [US]; LU DAN [US]; SURGULADZE DAVID [US]; T) 23 December 2009 (2009-12-23)
- D4 M HOFMANN ET AL: "Generation, selection and preclinical characterization of an Fc-optimized FLT3 antibody for the treatment of myeloid leukemia", LEUKEMIA, vol. 26, no. 6, 1 June 2012 (2012-06-01), pages 1228-1237, XP55041249
- D5 CHEN L ET AL: "Targeting FLT3 by chimeric antigen receptor T cells for the treatment of acute myeloid leukemia", LEUKEMIA, vol. 31, 2 June 2017 (2017-06-02), pages 1830-1834, XP002777770; preview online 12 May 2017 (2017-05-12)
- D6 JETANI HARDIKKUMAR ET AL: "CAR T-cells targeting FLT3 have potent activity against Pdoc FLT3-ITD+AML and act synergistically with the FLT3-inhibitor crenolanib", LEUKEMIA, vol. 32, no. 5, 5 February 2018 (2018-02-05), pages 1168-1179, XP036497310
- D7 WO 2017/173410 A1 (AMGEN INC [US]) 5 October 2017 (2017-10-05)
Pdoc
- D8 WO 2018/119279 A1 (US HEALTH [US]) 28 June 2018 (2018-06-28)
Edoc
- D9 B. PHILIP ET AL: "A highly compact epitope-based marker/suicide gene for easier and safer T-cell therapy", BLOOD, vol. 124, no. 8, 21 August 2014 (2014-08-21), pages 1277-1287, XP055229811
- D10 WO 2016/120216 A1 (CELLECTIS [FR]; RINAT NEUROSCIENCE CORP [US]) 4 August 2016 (2016-08-04)
- D11 WO 2014/011988 A2 (UNIV PENNSYLVANIA [US]) 16 January 2014 (2014-01-16)

V.2 Novelty (Article 33(2) PCT)

V.2.1 Prior art documents

Document D1 describes FTL3 directed CAR T cells used for treating cancer. Said CAR construct comprises an antigen binding domain of an anti-FLT3 antibody, i.e. 4G8, a hinge domain, a transmembrane domain, and an intracellular domain coupled to T cell 4-1BB (CD137) co-stimulatory and CD3-zeta activation domains (paragraphs [11]-[14], Figure 1). Furthermore, a linker may be located between the VH and VL of the anti-FLT3 antibody (paragraph [15]). The CAR construct comprises the suicide gene iCasp (paragraph [19]).

Document D2 describes CAR T cells targeting the FLT3 in human AML. D2 states that a single chain variable fragment (scFv) derived from a well-characterized anti-human FLT3 antibody coupled to T cell 4-1BB(CD137) co-stimulatory and CD3zeta activation domains (whole document).

Document D3 describes the anti-FLT3 antibodies designated EB10 and D4-3 binding an epitope in the domain D4 of FTL3 and the antibody designated NC7 binding an epitope in domain D5 of FTL3 (p. 11 l. 7-10). EB10 inhibits FL-induced phosphorylation and FTL3-mediated activation of downstream kinases (p. 40 l. 4 - p. 41 l. 18). Furthermore, EB10 inhibits cell proliferation of leukemia cells (p. 42 l. 13 - p. 43 l. 2). Finally, D3 shows that EB10, NC7 and D4-3 effectively treat leukemia xenografts (p. 45 l. 3 - p. 46 l. 30) and can be used in combination with methotrexate (p. 47 l. 7 - p. 48 l. 14).

Document D4 describes the anti-FLT3 antibodies designated 4G8 (binds domain D4) and BV10 (binds domain D2) (p. 1230 left-hand col. 6th paragraph).

Document D5 describes CAR T cells targeting FLT3 used for treating AML. Said CAR comprises CD28, a co-stimulatory signaling domain, CD3zeta and a FLT3-specific scFv originally derived from a hybridoma of the Reference 8 (RAPPOLE ET AL. 1997 describing the monoclonal anti-FLT3 antibody 4G8).

Intermediate document D6 describes CAR T cells targeting FLT3 comprising the scFv of 4G8. The anti-FLT3 antibody 4G8 interacts with domain D4 of FLT3 (abstract) The structure of the CAR is described on p. 1169 right-hand col. 2nd paragraph).

Intermediate document D7 describes CAR T cells targeting FLT3 (paragraphs [18]-[39]). The anti-FLT3 antibodies are designated 10E3, 2E7, 8B5, 4E9, 11F11 (paragraphs [221]-[270]).

E-document D8 describes anti-FLT3 antibodies (m1006, m1007, m1008, m1009 and m1012) and CAR constructs comprising said antibodies used targeting FLT3 in the treatment of AML (Examples 1 and 2 p. 47-51).

Document D9 describes a construct comprising a suicide gene such as RQR8 and its use as a safer and cheaper T cell gene therapy (abstract, p. 1278 left-hand col. 2nd paragraph). D9 teaches co-expression of RQR8 with a CAR (p. 1278 left-hand col. 3rd paragraph). Said RQR8 has two copies of the rituximab mimotope flanking the QBE10 epitope on the CD8 stalk (p. 1279 right-hand col. 2nd paragraph).

Document D10 describes a chimeric antigen receptor comprising a scFv (directed e.g. against CD135) and at least one mAb-specific epitope (e.g. of rituximab) (claims 1-17, 31).

Document D11 describes CAR constructs comprising bispecific scFvs (see entire document).

V.2.2 With respect to claims 1, 16-21, 32, 35, 43, 44, 46, 48, 51-66

The subject-matter of claims 1, 16-21, 32, 35, 43, 44, 46, 48, 51-66 is not novel in light of D1.

The subject-matter of claims 1, 16, 32, 35, 43, 44, 48, 51 is not novel in light of D5.

V.2.3 With respect to claims 2-15, 22-31, 33, 34, 36-42, 45, 47, 49, 50, 67-87

None of the cited prior art documents describes the subject-matter of claims 2-15 (i.e. the specific sequences of the anti-FLT3 antibodies), 22-31, 33, 34, 36-42, 45, 47, 49, 50, 67-87. Therefore, the subject-matter of claims 2-15, 22-31, 33, 34, 36-42, 45, 47, 49, 50, 67-87 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 2-15

The subject-matter of claims 2-15 differs from each of the closest prior art documents D1 or D5 in the sequence of the CDRs/VH/VL. The technical effect based on these differing sequences is not apparent from the application as originally filed since comparative data are missing.

Therefore, the technical problem to be solved may be regarded as providing alternative CAR constructs comprising a FLT3-binding domain.

The solution proposed in claims 2-15 of the present application cannot be considered involving an inventive step in the sense of Article 33(3) PCT for the following reasons:

Given the fact that methods to obtain monoclonal antibodies directed against any antigen (such as FLT3) and to screen such antibodies in order to select antibodies showing a desired property are routine in the art, and the skilled person would recognize the need of such alternative/further antibodies, the skilled person would consider obvious producing further anti-FLT3 antibodies comprised in CAR constructs

to solve the technical problem posed. In order to do so, the skilled person would only apply standard techniques. An inventive step could only be acknowledged if the antibodies (or the CAR construct comprising said antibody molecules) would show unexpected properties.

Hence the subject-matter of claims 2-15 is not considered inventive in the sense of Article 33(3) PCT.

V.3.2 With respect to claims 22-31, 33, 34, 36-42, 45, 47, 49, 50, 67-87

Claims 22-31, 33, 34, 36-42, 45, 47, 49, 50, 56, 67-87 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

V.4 Industrial Applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-87

The subject-matter of claims 1-87 appears to be susceptible of industrial application.

V.5 Further remarks

V.5.1 With respect to claims 59, 61-71, 78-87

The subject-matter of claims 59, 61-71, 78-87 is considered to be a method of treatment by therapy of the human or animal body.

For the assessment of the present claims 59, 61-71, 78-87 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. 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 59, 61-71, 78-87 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

V.5.2 With respect to claims 2-4, 7

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and

light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain regions in order to form functional antigen binding sites.

A claim to an antibody which is structurally characterised by less than the full sequence of all the CDRs, and their specific order, cannot be seen to sufficiently disclose an antibody with any particular properties (Articles 5 and 6).

V.5.3 With respect to claim 5

Claim 5 refers to 33 VH sequences and to 33 VL sequences. The CDRs of these VH/VL sequences differ from each other. It does not appear to be supported by the application that each combination of VH/VL results in a FLT3-binding scFv/antibody (Article 6 PCT). The application as originally filed describes specific VH/VL pairs forming together a FLT3-specific antibody.

Item VI

VI.1 With respect to documents D6-D8

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited documents D6-D7 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the documents D7-D8 could be relevant to the question of novelty.