PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)
(PCT Rule 44bis)

<table>
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<tr>
<th>Applicant’s or agent’s file reference</th>
<th>FOR FURTHER ACTION</th>
<th>See item 4 below</th>
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<th>International filing date (day/month/year)</th>
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<td>08 October 2015 (08.10.2015)</td>
<td>08 October 2014 (08.10.2014)</td>
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International Patent Classification (8th edition unless older edition indicated)
See relevant information in Form PCT/ISA/237

Applicant
NOVARTIS AG

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.
   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

   - [ ] Box No. I Basis of the report
   - [ ] 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
   - [x] Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis.2).

   Date of issuance of this report
   11 April 2017 (11.04.2017)

   Authorized officer
   Athina Nickitas-Etienne
   e-mail: pct.team4@wipo.int

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. +41 22 338 82 70

Form PCT/IB/373 (January 2004)
PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA220

PCT

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

Date of mailing
(day/month/year) see form PCT/ISA210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2015/054775

International filing date (day/month/year)
08.10.2015

Priority date (day/month/year)
08.10.2014

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

Applicant
NOVARTIS AG

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)(ii) 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/ISA220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of this opinion
see form
PCT/ISA210

Authorized Officer
Herrmann, Patrice
Telephone No. +49 89 2399-0

Form PCT/ISA237 (Cover Sheet) (January 2015)
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:
      - ☐ on paper or in the form of an image file.
   b. ☐ furnished together with the international application under PCT Rule 13ter.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 13ter.1(a)).
      - ☐ on paper or in the form of an image file (Rule 13ter.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:

   **see separate sheet**
1. Statement

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<td>Novelty (N)</td>
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<td>Inventive step (IS)</td>
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<td>1-58</td>
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<td>Industrial applicability (IA)</td>
<td>Claims</td>
<td>1-58</td>
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2. Citations and explanations

see separate sheet
Re Item I

Basis of the report
Sequences SEQ ID NOs 1-113 from the sequence listing are also included in the basis of this written opinion.

Re Item V

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

1  Reference is made to the following documents:


D5  WO 2006/105021 A2 (TOLERRX INC [US]; SMITH L MARY [US]; SZYMANSKA GRAZYNA [US]; PONATH PA) 5 October 2006 (2006-10-05)


D7  KO K ET AL: "TREATMENT OF ADVANCED TUMORS WITH AGONISTIC ANTI-GITR MAB AND ITS EFFECTS ON TUMOR-INFLTRATING FOXP3(+)CD25(+)CD4(+) REGULATORY T
None of the prior-art at hand discloses the subject-matters of present claims 1-58. Claims 1-58 appear therefore to meet the requirements of Article 33(2) PCT.

However, the subject-matters of claims 1-58 do not appear to be based on an inventive concept and claims 1-58 therefore lack an inventive step required to fulfill Articles 33(1) and (3) PCT, the reasons being as follows:


3.2 Document D1 can thus be considered to represent the closest state of the art for the subject-matter of present claims 1-38 The subject-matters of claims 1-38 differ from the disclosure of document D1 by the fact that particular human, humanized or chimeric anti-human GITR monoclonal antibodies are selected for use in medicine.

3.3 However the instant application is silent as to any particular effect linked to the use of said special anti-GITR antibodies.

3.4 Hence, in view of the closest state of the art at hand, the objective technical problem in the art that the subject-matters of claims 1-38 proposes to solve can be seen in the provision of alternative anti-human GITR monoclonal antibodies that can be used as therapeutic agents in the treatment of cancer.

3.5 The solution proposed in the instant claims, i.e. the particular antibodies used in therapy, is however not considered inventive because the procedure to obtain, screen and produce monoclonal antibodies specifically recognizing well known proteins such as human GITR is considered routine procedure for the skilled artisan. Therefore the production of alternative monoclonal antibodies directed against human GITR is considered to represent a routine procedure and, in the absence of evidence to the contrary, the claimed specific antibodies when used in therapy do not solve a previously unforeseeable technical problem and do not lead to any unexpected and surprising technical effect. Moreover the medical use of monoclonal antibodies specific for GITR in the treatment of cancer or for enhancing T cell
response in an individual in need thereof is already well known in the art (cf. D1 abstract, p. 2 paragraphs [0010]-[0021], p. 9 paragraph [0100] - p. 15 paragraph [0159], claims 1-20).

3.6 Moreover, humanization of known monoclonal antibodies useful in human therapy is considered to be a routine technique for the skilled artisan. Indeed, the specific improvements encountered by the use of said humanized monoclonal antibodies versus mouse monoclonal antibodies are very well known in the art.

3.7 Thus claims 1-38 do not appear to meet the requirements of Articles 33(1) and 33(3) PCT for lack of inventive step.

3.8 For identical reasons as those already mentioned herein above under points 3.1-3.7, the polynucleotides of claim 39 encoding the non-inventive antibodies of claim 1-35, and compositions of claims 40-41 or kit of claim 42 comprising the non-inventive antibodies of claims 1-35, in the absence of a clear indication of a hitherto unknown technical effect cannot be relied upon for the recognition of an inventive step. Furthermore, the use of said alternative, non-inventive, anti-GITR monoclonal antibodies for the treatment of cancer and for enhancing a T cell response in an individual in need thereof, as in claims 43-58, represents an obvious option the skilled person, aware of the teaching of D1, would select without involving inventive skills.

3.9 Hence claims 39-58 appear to lack inventive step contrary to the requirements of Articles 33(1) and 33(3) PCT.

3.10 An identical reasoning as that raised herein above under points 3.1-3.9 would apply mutatis mutandis to the subject-matters of claims 1-58 when departing from any of the documents D2-D7 each taken separately as closest state of the art. Each document D2-D7 discloses anti-GITR monoclonal antibody and its usefulness for reversing immune tolerance in anti-tumor therapy, for increasing immune response to vaccine and for the treatment of infectious diseases (cf. D2 abstract, p. 2 line 2 - p. 5 line 7, examples 1-10 and claims; D3 abstract, p. 2 paragraph [0008] - p. 4 paragraph [0020], examples 1-8 and claims; D4 abstract, p. 5 paragraph [0012] - p. 15 paragraph [0042], examples 1-16 and claims; D5 abstract, p. 1 line 35 - p. 8 line 7, examples 1-8 and claims; D6 abstract, p. 4905 left-hand column last but one full paragraph, p. 4905 right-hand column last full paragraph - p. 4909 left-hand column line 15, Fig. 1-6; D7 abstract, p. 886 right-hand column line 8 - p. 890 right-hand column first full paragraph, Fig. 1-5).
Hence, the subject-matters of claims 1-58 would also appear to lack inventive step in view of the disclosure of documents D2-D7 each considered separately as closest state of the art, contrary to the requirements of Articles 33(1) and 33(3) PCT.

4 Claim 42 lacks clarity contrary to the requirements of Article 6 PCT because it relates to a kit that comprises one single component whereas a kit should by definition correspond to the regrouping of distinct components into a box or a single case. This is however presently not the case for the subject-matter of claim 42 which amounts to claiming the single product per se and leaves therefore the skilled reader in doubt as to the exact claimed scope.

5 Claims 43-50 and 57 lack clarity contrary to the requirements of Article 6 PCT because the claims attend to achieve protection for the medical use of a particular product, wherein the pathological condition is defined functionally by the expression "method of enhancing a T cell response in an individual in need thereof". Said functional definition however does not correspond to well established pathological conditions and the instant application fails to give guidance in the form of experimental tests or testable criteria available in the application or in the prior art that would allow the person skilled in the art to recognise which pathological conditions fall within said functional definition, leaving therefore the skilled reader in doubt as to the exact intended scope of protection by said claims.

6 As regards claims 43-56 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 43-56 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.