

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

# 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.<br>PCT/IB2016/053285 | International filing date (day/month/year)<br>03.06.2016 | Priority date (day/month/year)<br>06.08.2015 |
|----------------------------------------------------|----------------------------------------------------------|----------------------------------------------|

International Patent Classification (IPC) or both national classification and IPC  
INV. A61K39/395 A61K31/7008 ADD. C07K16/28

Applicant  
GLAXOSMITHKLINE INTELLECTUAL PROPERTY...

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.

|                                                                                                                                                                                                                                                                                   |                                                                               |                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Name and mailing address of the ISA:</p>  <p>European Patent Office<br/>P.B. 5818 Patentlaan 2<br/>NL-2280 HV Rijswijk - Pays Bas<br/>Tel. +31 70 340 - 2040<br/>Fax: +31 70 340 - 3016</p> | <p>Date of completion of<br/>this opinion</p> <p>see form<br/>PCT/ISA/210</p> | <p>Authorized Officer</p> <p>Covone-van Hees, M</p> <p>Telephone No. +31 70 340-0</p>  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

---

**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:
    - ☒ 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 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:

---

**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 43bis.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 43bis.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>2-5, 7-11, 13, 15-18</u> |
|                               | No: Claims  | <u>1, 6, 12, 14, 19, 20</u> |
| Inventive step (IS)           | Yes: Claims |                             |
|                               | No: Claims  | <u>1-20</u>                 |
| Industrial applicability (IA) | Yes: Claims | <u>1-20</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

---

**Box No. VII Certain defects in the international application**

---

The following defects in the form or contents of the international application have been noted:

see separate sheet

---

**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 V**

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

- 1 Claims 11,14-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. Patentability, in particular novelty and inventive step, of these claims has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.
- 2 **Novelty** (Art.33(2) PCT)
  - 2.1 Kaczanowska et al. (**D1**) study the effect of TLR agonist in the treatment of cancer and suggest the combination with anti-OX40 or anti-4-1BB to potentiate T cell responses and synergistically enhance the cancer immune response (pg.858-859).
  - 2.2 WO2004060319 (**D2**) teaches the combination of TLR and TNFR superfamily agonists to synergistically enhance an immune response against cancer antigens. TLR4 and OX40 agonist are also mentioned (whole doc).
  - 2.3 WO03/045431 (**D3**) exemplifies a combination of TRL agonist in combination with OX40 antagonists to treat cancer (whole doc).
  - 2.4 Lee et al. (**D4**) discloses the combination of TRL agonists and OX40 agonists to enhance immunostimulation (whole doc).
  - 2.5 D1-D4 anticipate the subject-matter of claims 1,6,12,14,19,20 (Art.33(2) PCT).
- 3 **Inventive Step** (Art.33(3) PCT)
  - 3.1 WO2015095423 (**D5**) teaches the use of an anti-OX40 antibody (which has the same sequences as the anti-OX40 of present application) in combination with PD-1 agonist to treat cancer. The difference between claim 2 and the closest prior art is the use of TLR4 modulators instead of PD-1 agonist.
  - 3.2 There is no effect: both combinations enhance tumor therapy. The problem to be solved can therefore be seen in the provision of alternative OX-40 modulator combinations.
  - 3.3 The solution proposed in claim 2 is not inventive the reasons being the following: combination of TLR modulators and OX40 agonists is known from the prior art (e.g. D1, D2, D4). The skilled person would therefore regard it as

a normal option to replace PD-1 agonists with TLR4 modulators in order to solve the problem posed and without inventive skills.

- 3.4 Additionally, the applicants attention is brought to the fact that, if the monotherapies are known to be effective in the claimed treatment, a method of treatment wherein present agents are administered in a combined therapy does not per se rely on an inventive concept, unless that leads to unexpected advantages and/or effects. An inventive step may only be acknowledged if the combination therapy shows unexpected advantages e.g. synergism. Synergism is compound dependent and unless specifically shown, cannot be generalised to a class of compounds.
- 3.5 Remaining claims do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step: they are mainly standard alternatives in this technical field, which fall within the routine skills of those in the art, and which do not appear to lead to any surprising effects or advantages.

#### **Re Item VI**

##### **Certain documents cited**

Sagiv-Barfi et al 07.12.15

#### **Re Item VII**

##### **Certain defects in the international application**

- 3.6 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D5 is not mentioned in the description, nor is this document identified therein.

#### **Re Item VIII**

##### **Certain observations on the international application**

- 4 Claim 1 is not supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and drawings. Claim 1 broadly refers to OX40 and TLR4 modulators. The examples show however that the effect is achieved with OX40 and TLR4 agonist. Hence, claim 1 is not supported by the description as required by Article 6 PCT.
- 5 The expression "antigen binding protein" in claim 1 is unclear, since it may comprise even the ligand.