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(54) Title: METHODS OF TREATING AN INDIVIDUAL THAT HAS FAILED AN ANTI-PD-1/ANTI-PD-L1 THERAPY

(57) Abstract: Provided herein are methods of treating cancer in an individual that has failed an anti-PD1/PD-L1 therapy, comprising selecting an individual that has failed a prior anti-PD1/PD-L1 therapy; and administering to the individual a first agent that blocks or disrupts PD-L2, RGMb, or a combination thereof, and a second agent that blocks or disrupts PD-L1, PD-1 or a combination thereof. Also provided herein are kits and therapeutic compositions for use in the methods described herein.



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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 C07K16/22 C07K16/28
ADD. A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
C07K A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|---|
| X | <p>Miao Yu Rebecca ET AL: "Neutralizing PD-L1 and PD-L2 Enhances the Efficacy of Immune Checkpoint Inhibitors in Ovarian Cancer", bioRxiv, 20 January 2020 (2020-01-20), pages 1-39, XP055879264, DOI: 10.1101/2020.01.19.911941 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2020.01.19.911941v1.full.pdf [retrieved on 2022-01-14] the whole document paragraph [summary] page 8, last paragraph page 10, last paragraph - page 12, paragraph 1 page 11, paragraph 1</p> <p align="center">----- -/--</p> | <p>1-13, 19, 20, 26-61, 68, 74-99, 106, 117-149, 162-166</p> |

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

| | |
|---|---|
| <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> | <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> |
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| Date of the actual completion of the international search 1 March 2022 | Date of mailing of the international search report 16/05/2022 |
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| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016 | Authorized officer Siaterli, Maria |
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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|---|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | <p>WO 02/00730 A2 (GENETICS INST [US]; DANA FARBER CANCER INST INC [US]) 3 January 2002 (2002-01-03)</p> <p>page 124, line 20 - line 24; claim 50; figure 16; examples 4,5</p> <p>-----</p> | <p>1-13,19, 20, 26-61, 68, 74-99, 106, 117-149, 162-166</p> |
| X | <p>BROWN JULIA A ET AL: "Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production", THE JOURNAL OF IMMUNOLOGY, WILLIAMS & WILKINS CO, US, vol. 170, no. 3, 1 February 2003 (2003-02-01), pages 1257-1266, XP002973918, ISSN: 0022-1767 the whole document</p> <p>-----</p> | <p>1-13,19, 20, 26-61, 68, 74-99, 106, 117-149, 162-166</p> |
| X | <p>PAREKH VRAJESH V ET AL: "PD-1/PD-L Blockade Prevents Anergy Induction and Enhances the Anti-Tumor Activities of Glycolipid-Activated Invariant NKT Cells", THE JOURNAL OF IMMUNOLOGY, WILLIAMS & WILKINS CO, US, vol. 182, no. 5, 1 March 2009 (2009-03-01), pages 2816-2826, XP002552134, ISSN: 0022-1767, DOI: 10.4049/JIMMUNOL.0803648 page 2821, right-hand column, last paragraph; figures 3,5</p> <p>-----</p> | <p>1-13,19, 20, 26-61, 68, 74-99, 106, 117-149, 162-166</p> |
| X | <p>MIURA: "Blockade of B7-H1 or B7-DC induces an anti-tumor effect in a mouse pancreatic cancer model", INTERNATIONAL JOURNAL OF ONCOLOGY, vol. 35, no. 4, 1 September 2009 (2009-09-01), XP055052567, ISSN: 1019-6439, DOI: 10.3892/ijo_00000387 the whole document page 742, right-hand column, paragraph 3 - page 743, left-hand column, paragraph 1 page 743, right-hand column, last paragraph - page 745, left-hand column, paragraph 1; figure 2 page 748</p> <p>-----</p> | <p>1-13,19, 20, 26-61, 68, 74-99, 106, 117-149, 162-166</p> |

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out 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).
2. 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.
3. Additional comments:

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
1-13, 19, 20, 26-61, 68, 74-99, 106, 117-149, 162-166 (all partially)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-13, 19, 20, 26-61, 68, 74-99, 106, 117-149, 155, 156, 162-166(all partially)

The claims of present application refer to

a) agent that blocks or disrupts PD-L2

b) agent that blocks or disrupts PD-L1

Thus, they encompass several compounds defined only by their desired functions, contrary to the requirement of clarity in Article 6 PCT, because the "result-to-be-achieved" type of definition does not allow the scope of the claim to be ascertained. The claims don't even require that the compounds bind to the targets. The "blocking or disruption" may be achieved indirectly. The fact that any compound could be screened does not overcome this objection, as the skilled person would not know beforehand whether it fell within the scope claimed, except for the compounds disclosed in the description i.e. antibodies (see examples). Undue experimentation would be required to screen compounds randomly. Present claims relates to an extremely large number of possible compounds/methods. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the methods claimed, see examples: anti PD-L2 and anti PD-L1 antibodies .

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-13, 19, 20, 26-61, 68, 74-99, 106, 117-149, 162-166(all partially)

treatment of cancers with anti PD-L2 and anti PD-L1 inhibitors

2. claims: 1-13, 19, 21-25, 31-61, 69-99, 107-135, 138-149, 157-161(all partially)

treatment of cancers with anti PD-L2 and anti PD-1 inhibitors

3. claims: 1-4, 14-20, 26-52, 62-68, 79-89, 100-106, 117-140, 150-156, 162-166(all partially)

treatment of cancers with anti RGMb and anti PD-L1 inhibitors

4. claims: 1-4, 14-19, 21-25, 31-52, 62-67, 69-73, 79-89, 100-135, 138-140, 150-161(all partially)

treatment of cancers with anti RGMb and anti PD-1 inhibitors

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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