

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 25131		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US22/23250	International filing date <i>(day/month/year)</i> 04 April 2022 (04.04.2022)	(Earliest) Priority Date <i>(day/month/year)</i> 08 April 2021 (08.04.2021)	
Applicant MERCK SHARP & DOHME CORP.			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 2

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

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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:

3. ☒ Claims Nos.: 6-77
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:
-***-Please See Supplemental Page-***-

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 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.: 1-5, and SEQ ID NOs: 1, 2, 3 (LC-CDRs 1, 2, 3), SEQ ID NOs: 6, 7, 8 (HC-CDRs 1, 2, 3).

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.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 47/02; A61K 39/395; A61P 35/00 (2022.01)

ADD. C07K 16/28 (2022.01)

CPC - INV. A61K 47/02; A61K 39/395; A61K 39/39541; A61P 35/00; C07K 16/28

ADD. A61K 9/0019; A61K 2039/505; A61K 2039/507; A61K 2039/545; C07K 2317/565

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2020/097141 A1 (MERCK SHARP & DOHME CORP.) 14 May 2020; claim 52; page 54, lines 4-5; page 54, lines 6-7	1-5
Y	WO 2018/223182 A1 (THE COUNCIL OF THE QUEENSLAND INSTITUTE OF MEDICAL RESEARCH) 13 December 2018; page 75, line 39 to page 76, line 14	1-5
Y	US 2021/0047409 A1 (LALA, M et al.) 18 February 2021; paragraph [0079]	5
Y	(AKALA, BO ET AL.). "AACR 2021 KEYNOTE-555: pembrolizumab bioavailability after subcutaneous administration in melanoma." Video transcript (online). AACR. Retrieved From The Internet: [URL: https://www.vjncology.com/video/qf9dtmtiwm0-keynote-555-pembrolizumab-bioavailability-aft-er-subcutaneous-administration-in-melanoma/]. 07 April 2021; page 2, seventh paragraph	3-4

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

08 July 2022 (08.07.2022)

Date of mailing of the international search report

SEP 08 2022

Name and mailing address of the ISA/US

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---Continued From Box No. III: Observations where unity of invention is lacking---

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-5, and SEQ ID NOs: 1, 2, 3 (LC-CDRs 1, 2, 3), SEQ ID NOs: 6, 7, 8 (HC-CDRs 1, 2, 3) are directed towards an anti-PD1 antibody and methods associated therewith.

The anti-PD1 antibody and methods of Claims 1-5 (each in-part) are believed to encompass the first named invention of Groups I+ and are the claims that will be searched without fee to the extent that they SEQ ID NOs: 1, 2, 3 (first exemplary LC-CDRs 1, 2, 3), SEQ ID NOs: 6, 7, 8 (first exemplary HC-CDRs 1, 2, 3). This first named invention of Group I+ has been selected to encompass the first species of each of the genus found in claims 1 and 2 based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines.

Applicant is invited to elect additional LC-CDR(s) 1, 2, 3, HC-CDR(s) 1, 2, 3 to be searched. Additional LC-CDR(s) 1, 2, 3, HC-CDR(s) 1, 2, 3 will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected LC-CDR(s) 1, 2, 3, HC-CDR(s) 1, 2, 3. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. Exemplary elections would be SEQ ID NOs: 11, 12, 13 (LC-CDRs 1, 2, 3), SEQ ID NOs: 14, 15, 16 (HC-CDRs 1, 2, 3).

Groups I+ were considered to share the technical features including: a method of treating cancer in a human patient comprising subcutaneously administering to the patient about 280 mg to about 450 mg of an anti-PD-1 antibody, or antigen binding fragment thereof, every approximately three weeks, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: a. light chain or LC complementarity determining regions or CDRs LC-CDR1, LC-CDR2 and LC-CDR3 sequences, and heavy chain or HC CDRs HC-CDR1, HC-CDR2 and HC-CDR3 sequences; a method of treating cancer in a human patient comprising subcutaneously administering to the patient approximately every three weeks a dose of an anti-PD-1 antibody, or antigen binding fragment thereof, that is at least 1.6 times higher than a 200 mg or a 2 mg/kg dose of the anti-PD-1 antibody, or antigen binding fragment thereof, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: a. light chain or LC complementarity determining regions or CDRs LC-CDR1, LC-CDR2 and LC-CDR3 sequences, and heavy chain or HC CDRs HC-CDR1, HC-CDR2 and HC-CDR3 sequences; these shared technical features are previously disclosed by the publication entitled "Assessment of Subcutaneous vs Intravenous Administration of Anti-PD-1 Antibody PF-06801591 in Patients With Advanced Solid Tumors A Phase 1 Dose-Escalation Trial" by Johnson, et al. (hereinafter 'Johnson') in view of WO 2018/222711 A2 to Bristol-Myers Squibb Company (hereinafter 'Bristol').

Johnson discloses a method of treating cancer in a human patient comprising subcutaneously administering to the patient about 280 mg to about 450 mg of an anti-PD-1 antibody, or antigen binding fragment thereof, every approximately four weeks, rather than three weeks (method of treating cancer patients comprising administering a subcutaneous dose of 300 mg every 4 weeks; abstract), wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: a. light chain or LC complementarity determining regions or CDRs LC-CDR1, LC-CDR2 and LC-CDR3 sequences, and heavy chain or HC CDRs HC-CDR1, HC-CDR2 and HC-CDR3 sequences (the anti-PD-1 antibody is a humanized immunoglobulin G4 monoclonal antibody, which intrinsically comprises LC-CDRs 1-3 and HC-CDRs 1-3; page 1000, 1st column, 2nd paragraph); a method of treating cancer in a human patient comprising subcutaneously administering to the patient approximately every four, rather than three weeks, a dose of an anti-PD-1 antibody, or antigen binding fragment thereof, that is at least 1.6 times higher than a 200 mg or a 2 mg/kg dose of the anti-PD-1 antibody (method of treating cancer patients comprising administering a subcutaneous dose of 300 mg every 4 weeks, wherein 300 mg is higher than 1.6 times a 2 mg/kg dose of the anti-PD1 antibody for an average 70 kg patient; abstract), or antigen binding fragment thereof, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: a. light chain or LC complementarity determining regions or CDRs LC-CDR1, LC-CDR2 and LC-CDR3 sequences, and heavy chain or HC CDRs HC-CDR1, HC-CDR2 and HC-CDR3 sequences (the anti-PD-1 antibody is a humanized immunoglobulin G4 monoclonal antibody, which intrinsically comprises LC-CDRs 1-3 and HC-CDRs 1-3; page 1000, 1st column, 2nd paragraph).

Johnson does not disclose administering the anti-PD-1 antibody every approximately three weeks.

Bristol discloses subcutaneously administering an anti-PD-1 antibody every approximately three weeks (anti-PD1 antibody can be administered subcutaneously once every three weeks; paragraphs [0013], [0141], [0154]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Johnson, for the integration of subcutaneously administering an anti-PD-1 antibody every approximately three weeks, as previously disclosed by Bristol, as the previous disclosure by Johnson includes a method of treating cancer in a human subject comprising subcutaneously administering a specified dose of an anti-PD1 antibody to the subject, the Bristol reference discloses subcutaneously administering an anti-PD-1 antibody every approximately three weeks, and this combination would provide a method for treating cancer in a human patient by subcutaneously administering to the patient a therapeutically effective dose of an anti-PD1 antibody once every three weeks, wherein the three week time interval ensures optimal tolerability towards the antibody, and the subcutaneous administration provides an improvement over conventional intravenous administration in terms of patient satisfaction, cost, and resource use.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Johnson and Bristol references, unity of invention is lacking.