

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: Sarah L. Hooson
Merck Sharp & Dohme Corp.
126 East Lincoln Avenue
Rahway, NJ 07065-0907
United States Of America

Date of mailing
(day/month/year)

SEP 08 2022

Applicant's or agent's file reference
25131

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US22/23250

International filing date (day/month/year)

04 April 2022 (04.04.2022)

Priority date (day/month/year)

08 April 2021 (08.04.2021)

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

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

Applicant MERCK SHARP & DOHME CORP.

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 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.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

08 July 2022 (08.07.2022)

Authorized officer

Shane Thomas

PCT Help Desk

Telephone No. 571-272-4300

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US22/23250

Box No. I Basis of this 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(b)).
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:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US22/23250

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6-77

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 6-77 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 6-77 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 6-77

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US22/23250

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest and, where applicable, the protest fee.
 - ☐ paid additional fees under protest but the applicable protest fee was not paid.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:

-Please See Supplemental Page-

4. Consequently, this opinion has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to 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).

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US22/23250

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

1. Statement

Novelty (N)	Claims	1-5	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-5	NO
Industrial applicability (IA)	Claims	1-5	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-2 lack an inventive step under PCT Article 33(3) as being obvious over WO 2020/097141 A1 to MERCK SHARP & DOHME CORP. (hereinafter "Merck") in view of WO 2018/223182 A1 to THE COUNCIL OF THE QUEENSLAND INSTITUTE OF MEDICAL RESEARCH (hereinafter "Queensland").

As per claim 1, Merck discloses a method of treating cancer in a human patient comprising subcutaneously administering to the patient (the anti-human PD-1 antibody formulation is administered by subcutaneous administration; claim 52) about 280 mg to about 450 mg of an anti-PD-1 antibody, or antigen binding fragment thereof (dosing regimen comprises administering a dose of 1, 2, 3, or 10 mg/kg of any of the pharmaceutical formulations described herein; page 54, lines 4-5), every approximately three weeks (the interval between doses is about 21 days, +/-2 days; page 54, lines 6-7). Merck does not disclose wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: (a) light chain (LC) complementarity determining regions (CDRs) LC-CDR1, LC-CDR2 and LC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3, respectively; and heavy chain (HC) CDRs HC-CDR1, HC-CDR2 and HC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 6, 7 and 8, respectively wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: (a) light chain (LC) complementarity determining regions (CDRs) LC-CDR1, LC-CDR2 and LC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3, respectively. Queensland discloses wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: (a) light chain (LC) complementarity determining regions (CDRs) LC-CDR1, LC-CDR2 and LC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3, respectively (SEQ ID NOs: 1, 2, and 3 of PCT application are 100% identical to amino acid residues 155-169, 185-191, and 224-232, respectively, of variable light chain amino acid sequence of anti-PD-1 MAb pembrolizumab, SEQ ID NO: 222; page 75, line 39 to page 76, line 14), and heavy chain (HC) CDRs HC-CDR1, HC-CDR2 and HC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 6, 7 and 8, respectively (SEQ ID NOs: 6, 7, and 8 of PCT application are 100% identical to amino acid residues 155-169, 185-191, and 224-232, respectively, of variable light chain amino acid sequence of anti-PD-1 MAb pembrolizumab, SEQ ID NO: 222; page 75, line 39 to page 76, line 14). It would have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the method of treating cancer using subcutaneous administration of anti-PD-1, as previously disclosed by Merck, with variable light and heavy chain amino acid sequence of Mab pembrolizumab, as previously disclosed by Queensland, to provide the benefit of targeting cancer in a human patient using a novel subcutaneous dosing regimen combined with a known anti-cancer drug for increased flexibility and convenience in treatment.

As per claim 2, Merck discloses a method of treating cancer in a human patient comprising subcutaneously administering to the patient (the anti-human PD-1 antibody formulation is administered by subcutaneous administration; claim 52) approximately every three weeks (the interval between doses is about 21 days, +/-2 days; page 54, lines 6-7) a dose of an anti-PD-1 antibody, or antigen binding fragment thereof (a formulation comprising pembrolizumab; page 53, lines 32-34), 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 (the dosing regimen comprises administering a dose of 1, 2, 3, or 10 mg/kg of any of the pharmaceutical formulations described; page 54, lines 4-5). Merck does not disclose wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: (a) light chain (LC) complementarity determining regions (CDRs) LC-CDR1, LC-CDR2 and LC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3, respectively; and heavy chain (HC) CDRs HC-CDR1, HC-CDR2 and HC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 6, 7 and 8, respectively wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: (a) light chain (LC) complementarity determining regions (CDRs) LC-CDR1, LC-CDR2 and LC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3, respectively. Queensland discloses wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises: (a) light chain (LC) complementarity determining regions (CDRs) LC-CDR1, LC-CDR2 and LC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3, respectively (SEQ ID NOs: 1, 2, and 3 of PCT application are 100% identical to amino acid residues 155-169, 185-191, and 224-232, respectively, of variable light chain amino acid sequence of anti-PD-1 MAb pembrolizumab, SEQ ID NO: 222; page 75, line 39 to page 76, line 14), and heavy chain (HC) CDRs HC-CDR1, HC-CDR2 and HC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 6, 7 and 8, respectively (SEQ ID NOs: 6, 7, and 8 of PCT application are 100% identical to amino acid residues 155-169, 185-191, and 224-232, respectively, of variable light chain amino acid sequence of anti-PD-1 MAb pembrolizumab, SEQ ID NO: 222; page 75, line 39 to page 76, line 14). It would have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the method of treating cancer using subcutaneous administration of anti-PD-1, as previously disclosed by Merck, with variable light and heavy chain amino acid sequence of Mab pembrolizumab, as previously disclosed by Queensland, to provide the benefit of targeting cancer in a human patient using a novel subcutaneous dosing regimen combined with a known anti-cancer drug for increased flexibility and convenience in treatment.

-Continued in Supplemental Box-

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US22/23250

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

-Continued From Box IV (ii): Lack of unity of invention--

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.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US22/23250

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

-Continued From Box V. 2: Citations and Explanations-

Claims 3-4 lack an inventive step under PCT Article 33(3) as being obvious over Merck and Queensland in further view of the publication entitled "AACR 2021 | KEYNOTE-555: pembrolizumab bioavailability after subcutaneous administration in melanoma" by Akala, B. et al. (hereinafter "Akala").

As per claim 3, Merck and Queensland disclose, in combination, the method of claim 1 or 2, Merck does not disclose wherein the bioavailability of the anti-PD-1 antibody, or antigen binding fragment thereof, is at least 64%. Akala discloses where the bioavailability of the anti-PD-1 antibody, or antigen binding fragment thereof, is at least 64% (the analysis showed that subcutaneous administration of pembrolizumab with an estimated bioavailability of 66%; page 2, seventh paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the method of treating cancer using subcutaneous administration of anti-PD-1, as previously disclosed by Merck, with the subcutaneously administered drug being pembrolizumab, as previously disclosed by Akala, to provide the benefit of targeting cancer in a human patient using a novel subcutaneous dosing regimen combined with subcutaneous drug delivery for increased flexibility in treatment while retaining potency.

As per claim 4, Merck and Queensland disclose, in combination, the method of claim 1 or 2, Merck does not disclose wherein the bioavailability of the anti-PD-1 antibody, or antigen binding fragment thereof, is at least 66%. Akala discloses where the bioavailability of the anti-PD-1 antibody, or antigen binding fragment thereof, is at least 66% (the analysis showed that subcutaneous administration of pembrolizumab with an estimated bioavailability of 66%; page 2, seventh paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the method of treating cancer using subcutaneous administration of anti-PD-1, as previously disclosed by Merck, with the subcutaneously administered drug being pembrolizumab, as previously disclosed by Akala, to provide the benefit of targeting cancer in a human patient using a novel subcutaneous dosing regimen combined with subcutaneous drug delivery for increased flexibility in treatment while retaining potency.

Claim 5 lacks an inventive step under PCT Article 33(3) as being obvious over Merck and Queensland in further view of US 2021/0047409 A1 to Lala, M. et al. (hereinafter "Lala").

As per claim 5, Merck and Queensland disclose, in combination, the method of claim 2, Merck does not disclose wherein the dose is 1.9 times higher than a 200 mg or a 2 mg/kg dose of the anti-PD-1 antibody, or antigen binding fragment thereof. Lala discloses wherein the dose is 1.9 times higher than a 200 mg or a 2 mg/kg dose of the anti-PD-1 antibody, or antigen binding fragment thereof (when referring to the dosage of "about 400 mg" the dosage can be from 360 mg to 440 mg; paragraph [0079]). It would have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the method of treating cancer using subcutaneous administration of anti-PD-1, as previously disclosed by Merck, with the higher dosage regimen of anti-PD-1 to patients, as previously disclosed by Lala, to provide the benefit of targeting cancer in a human patient using a novel regimen of a known anti-cancer drug with the higher dosage and lower frequency of administration for increased flexibility and convenience in treatment.

Claims 1-5 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.