PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2016/082745	28.12.2016	29.12.2015

International Patent Classification (IPC) or both national classification and IPC
INV. G01N33/574

Applicant
INSERM (INSTITUT NATIONAL DE LA SANTE ET DE LA...

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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Wiesner, Martina Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2016/082745

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 43*bis*.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 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:

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 43*bis*.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 43*bis*.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:

   see separate sheet

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. 1-15(partially)

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. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ 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 the whole application or for said claims Nos. 1-15(partially)

☐ 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 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

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:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-15(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15(partially)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15(partially)
Industrial applicability (IA)	Yes:	Claims	1-15(partially)
	No:	Claims	

2. Citations and explanations

   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

1 Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D1 Zoran Gatalica ET AL: "Programmed death 1 (PD-1) lymphocytes and ligand (PD-L1) in colorectal cancer and their relationship to microsatellite instability status.", J Clin Oncol, vol. 32, no. 5s, 30 May 2014 (2014-05-30), XP055199884

D2 Nicolas Jose Llosa ET AL: "Immune checkpoints expression in MSI versus MSS colorectal cancers and their potential therapeutic implications", J Clin Oncol, vol. 32, 1 May 2014 (2014-05-01), page 5s, XP055273851

D3 G. Brandacher: "Prognostic Value of Indoleamine 2,3-Dioxygenase Expression in Colorectal Cancer: Effect on Tumor-Infiltrating T Cells", CLINICAL CANCER RESEARCH, vol. 12, no. 4, 15 February 2006 (2006-02-15), pages 1144-1151, XP055273302

D4 Pin Wu ET AL: "PD-L1 and Survival in Solid Tumors: A Meta-Analysis", PLOS ONE, vol. 10, no. 6, 26 June 2015 (2015-06-26), page e0131403, XP055273298

D5 NICOLÁS J LLOSA ET AL: "Immune checkpoints in MSI and CSI colorectal cancers and their translational implications", JOURNAL FOR IMMUNOTHERAPY OF CANCER, BIOMED CENTRAL LTD, LONDON, UK, vol. 1, no. Suppl 1, 7 November 2013 (2013-11-07), page P161, XP021167111

D6 Y. Xiao ET AL: "The Microsatellite Instable Subset of Colorectal Cancer Is a Particularly Good Candidate for Checkpoint Blockade Immunotherapy", CANCER DISCOVERY, vol. 5, no. 1, 1 January 2015 (2015-01-01), pages 16-18, XP055271983

D7 N. J. LLOSA ET AL: "The Vigorous Immune Microenvironment of Microsatellite Instable Colon Cancer Is Balanced by Multiple Counter-Inhibitory Checkpoints", CANCER DISCOVERY, vol. 5, no. 1, 1 January 2015 (2015-01-01), pages 43-51, XP055349318

D8 NICOLASL LOSA ET AL: "The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints", JOURNAL FOR IMMUNOTHERAPY OF CANCER, BIOMED CENTRAL LTD, LONDON, UK, vol. 3, no. 2, 4 November 2015 (2015-11-04), page 1, XP021235584

Re Item II

2 **Priority**

The current application claims priority from EP 15307157 (P). Regarding the content of P the claimed priority is, at least in part, considered invalid. P only concerns the use of immune checkpoint proteins as markers in microsatellite unstable **colon** cancer. No basis for generalisation is directly and unambiguously derivable from P for e.g. methods for predicting the survival time of patients suffering from a microsatellite unstable cancer in general. For the subject-matter not present in P the international filing date (28.12.2016) will be considered as the effective date for examination of novelty and inventive step.

Re Item IV

3 **Non-unity**

According to the description the technical problem to be solved in the present application is the provision of methods for predicting survival time of patients suffering from a microsatellite unstable cancer and the provision of methods for predicting the response to treatment with an immune checkpoint inhibitor in patients suffering from a microsatellite unstable cancer. The solution is the use of an immune checkpoint protein as marker. The single general concept is the use of an immune checkpoint protein as a marker as a predictive marker in patients suffering from a microsatellite unstable cancer

However, D1, D2 and D5 already disclose this single general concept.

D1 (abstract) teaches that PD-1 activation by its ligand PD-L1 (CD274) plays a role in cancer progression and that it is widely expressed in many cell types in tumor microenvironment. D1 furthermore states that the inhibition of PD-1/ PD-L1 showed no benefit in colorectal cancers (CRC) in clinical trials. Document D1 discloses that PD-L1+ cancer cells are more common in microsatellite instability-high (MSI-H) cancers than in microsatellite stable (MSS) cancers and and teaches that the presence of cancer cell specific PD-L1 expression therefore should be considered before immune checkpoint therapies initiation. PD-L1 expression is also known as being associated with worse survival in solid tumors (see also D4 (abstract)).

Document D2 (abstract) discloses that microsatellite unstable colorectal cancers show high expression of IFN-γ-driven immune checkpoints such as PD-1, PD-L1, IDO-1 and INOS compared with MSS. D2 furthermore teaches that the expression of e.g. PD-L1 and IDO-1 could be targeted to enhance clinical benefit and be predictive of response to immune checkpoint inhibitors. IDO-1 and PD-L1 are furthermore well known predictors for shorter patient survival (see e.g. D3 (abstract), D4 (abstract)).

Document D5 (abstract) analysis the expression of the immune checkpoint proteins PD-1, TIM-3 and LAG3 on on tumor-infiltration T-cells from MSIhigh and MSIlow patients. D5 shows that the IFN-γ production is not inhibited in T-cells with high PD-1 expression except in the presence of high levels of Lag-3 and a PD-1 low CD4 population. D5 therefore concludes that patients with low expression of PD-1 may benefit form a LAG-3 or TIM-3 blockade approach.

In the light of D1, D2 (D2 in combination with either D3 or D4 with regard a method for predicting survival time) or D5, the above identified single general concept is not novel and inventive and thus cannot be the single general concept as required by Rule 13.1 PCT. The present application is therefore considered not to fulfil the requirement of unity as laid down in Rule 13.1 PCT.

No other technical feature could be identified which could be considered as a special technical feature within the meaning of Rule 13.2 PCT.

Consequently the groups of inventions are split up as follows:

Invention 1: Claims 1-15 (all partial)

Method for predicting the survival time of a patient suffering from a microsatellite unstable colorectal cancer and a method for determining whether a patient suffering from a microsatellite unstable colorectal cancer will achieve a response with an immune checkpoint inhibitor comprising i) determining the expression level of the gene encoding for IDO-1 in a tumor tissue sample obtained from the patient, and ii) comparing the expression level determined at step i) with a predetermined reference value; and a method of treating the thus identified patients.

Invention 2-15: Claims 1-15(all partial)

Method for predicting the survival time of a patient suffering from a microsatellite unstable colorectal cancer and a method for determining whether a patient suffering from a microsatellite unstable colorectal cancer will achieve a response with an immune checkpoint inhibitor comprising i) determining the expression level of at least one gene selected from the group consisting of CD40, CD274, ICOS, TNFRSF9, TNFRSF18, LAG3, IL2RB, HAVCR2, TNFRSF4, CD276, CTLA4, PDCD1LG2, VTCN 1 and PDCD 1 in a tumor tissue sample obtained from the patient, and ii) comparing the expression level determined at step i) with a predetermined reference value; and a method of treating the thus identified patients.

Complete searches for the other inventions represent substantive extra search burden. The first claimed invention mentioned in the claims has been searched (Invention 1 (claims 1-15 (all partial)).

Re Item V

Invention 1 (claims 1-15 (all partial))

4 **Inventive step**

The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 1-15 does not involve an inventive step.

4.1 Document D3 (whole document) is considered to be the prior art closest to the subject-matter of claim 1 and discloses IDO-1 (IDO, Indoleamine 2,3-Dioxygenase) as biomarker for shorter patients survival, including patients suffering from colorectal cancer.

The additional technical feature of claim 1 over D3 is the use of the marker to predict the survival time of MSI colorectal cancer

The technical effect of the invention is the prediction of survival time in a subset of patients suffering from MSI colorectal cancer.

The problem to be solved by the present invention may therefore be regarded as the provision of a further use of the biomarker IDO-1.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

D2 (abstract) already teaches that IDO-1 is upregulated in MSI colorectal cancers (CRCs).

D6 (whole document) also teaches that high expression of IDO-1 distinguishes MSI from microsatellite stable colorectal cancer.

D7 (figures 2; page 49, right-hand column, §2) and D8 (abstract) likewise teach that IDO and other immune checkpoint markers are highly upregulated in MSI tumors relative to MSS.

Hence, knowing from D2 and D6 to D8 that mainly MSI tumors express IDO-1, it would be obvious for the skilled person to use IDO-1 as predictor for survival time especially in patients with MSI colorectal cancer, since this is the type of colorectal cancer which can show high expression of the biomarker whereas microsatellite stable CRCs are mostly $IDO1^-$.

4.2 Document D1 (abstract) is considered to be the prior art closest to the subject-matter of claim 7 and teaches that PD-1 activation by its ligand PD-L1 (CD274) plays a role in cancer progression and that it is widely expressed in many cell types in tumor microenvironment. D1 furthermore states that the inhibition of PD-1/PD-L1 showed no benefit in colorectal cancers (CRC) in clinical trials. D1 discloses that PD-L1+ cancer cells are more common in microsatellite instability-high (MSI-H) cancers than in microsatellite stable (MSS) cancers and and teaches that the presence of cancer cell specific PD-L1 expression therefore should be considered before immune checkpoint therapies initiation.

The additional technical feature of claim 7 over D1 is the use of the marker IDO-1 for determining whether a patient suffering from a microsatellite unstable colorectal cancer will achieve a response with an immune checkpoint inhibitor.

The technical effect of the invention is not known.

The problem to be solved by the present invention may therefore be regarded as the provision of a further method for determining whether a patient suffering from a microsatellite unstable colorectal cancer will achieve a response with an immune checkpoint inhibitor.

The solution proposed in claim 7 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

D2 (abstract) already teaches that IDO-1 is upregulated in MSI CRCs. D2 furthermore proposes that the expression of IDO-1 could be used to predict the response to immune checkpoint inhibitors.

D6 (whole document) also teaches that high expression of IDO distinguishes MSI from microsatellite stable colorectal cancer. D5 furthermore teaches that small-molecule IDO pathway inhibitors are in development or in clinical trials.

D8 (abstract) teaches that IDO and other immune checkpoint markers are highly upregulated in MSI tumors relative to MSS. D8 suggest that blockade of specific checkpoints may be selectively efficacious in the MSI subset.

Hence, it would be obvious for the skilled person to use IDO-1 as a biomarker to determine if patients with MSI CRC will profit from the treatment with a competitive inhibitor of IDO-1, especially since D2 already already suggests the expression level of IDO-1 as predictor of response to immune checkpoint inhibitors in MSI CRC

4.3 The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claim 14, which therefore are also considered not inventive.

4.4 Dependent claims 2-6, 8-13 and 15 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, said features are either present in D1-D8 with the same context or represent standard modifications the skilled person would contemplate without exerting any inventive skill.

Re Item VIII

5 Although the claims 1, 7 and 14 concern all microsatellite unstable cancers, the application provides support and disclosure in terms of Articles 5 and 6 PCT only for microsatellite unstable colorectal cancer. Claims 1, 7 and 14 lack therefore support and disclosure in terms of Articles 5 and 6 PCT, since the skilled person after reading the description, would not be able to perform the invention over the whole area claimed without undue burden.