PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	28 FEB 2020

Applicant's or agent's file reference	FOR FURTHER ACTION
141962-00502	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 19/62992	25 November 2019 (25.11.2019)	28 November 2018 (28.11.2018)

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

IPC - A61K 31/7068; A61P 35/00; A61P 9/00 (2020.01)

CPC - A61K 31/7068; A61P 35/00; A61K 9/0019

Applicant
EVOL SCIENCE LLC

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 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 66.1*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/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	20 February 2020	Lee Young PCT Help Desk Telephone No. 571-272-4300

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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:

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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. 5-8, 10-13, 18-22, 31, 35-36, 40

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. 5-8, 10-13, 18-22, 31, 35-36, 40 are so unclear that no meaningful opinion could be formed *(specify)*:

because they 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. 5-8, 10-13, 18-22, 31, 35-36, 40

☐ 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.

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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**

1. Statement

Novelty (N)	Claims	9, 15-17, 24-27, 30, 32-34, 37-39, 41-42	YES
	Claims	1-4, 14, 23, 28-29	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-4, 9, 14-17, 23-30, 32-34, 37-39, 41-42	NO
Industrial applicability (IA)	Claims	1-4, 9, 14-17, 23-30, 32-34, 37-39, 41-42	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-4, 14, 23 and 28-29 lack novelty under PCT Article 33(2) as being anticipated by a document entitled "Rational combination therapy with PARP and MEK inhibitors capitalizes on therapeutic liabilities in RAS mutant cancers" to Sun et al. (hereinafter Sun).

Regarding Claim 1, Sun discloses a method of treating a solid metastatic or non-metastatic tumor in a subject (pg. 1, abstract: in patients with RAS mutant tumors) comprising administering (pg. 14, Fig. 8: injected into athymic nude mice subcutaneously) to the subject a PARP inhibitor and a MAPK activator (pg. 1, abstract: Synergistic activity of PARP and MEK inhibitor combinations) (MEK inhibitors are MAPK activators as evidenced by instant specification, para [0028]).

Regarding Claim 2, Sun discloses the method of claim 1 (pg. 1, abstract), wherein the tumor has a genotype of a mutated RAS (pg. 1, abstract: in patients with RAS mutant tumors).

Regarding Claim 3, Sun discloses the method of claim 2 (pg. 1, abstract), wherein the RAS mutation is RAS G12 mutation (pg. 5, left col, para 2: KRAS (G12V and G12C)).

Regarding Claim 4, Sun discloses the method of claims 1-3, as disclosed above, wherein the PARP inhibitor is talazoparib (pg. 6, Fig. 3: PARPi (BMN673; pg. 2, para 3: BMN673 (talazoparib), a potent trapping PARPi).

Regarding Claim 14, Sun discloses the method of claim 1 (pg. 1, abstract), wherein the PARP inhibitor and the MAPK activator are administered sequentially, simultaneously, or in an overlapping manner (pg. 13, right col, para 1: PARPi and MEKi combination, in vivo) (any combination is inherently one of sequentially, simultaneously, or overlapping combinations).

Regarding Claim 23, Sun discloses the method of claim 1 (pg. 1, abstract), wherein the tumor does not increase in size after the administration step (pg. 11, right col, para 4: Once again, MEKi and PARPi combinations markedly decreased tumor growth).

Regarding Claim 28, Sun discloses a pharmaceutical composition comprising a PARP inhibitor and a MAPK activator (pg. 14, Fig. 8: vehicle (0.5% hydroxypropylmethylcellulose and 0.2% Tween 80), ... the combination of BMN673 and GSK1120212B) (GSK1120212B is a MEK inhibitor, (pg. 2, para 1: GSK1120212B (MEKi)); BMN673 is a PARP inhibitor (pg. 2, para 3: BMN673 (talazoparib), a potent trapping PARPi)) (MEK inhibitors are MAPK activators as evidenced by instant specification, para [0028]).

Regarding Claim 29, Sun discloses the pharmaceutical composition of claim 28 (pg. 14, Fig. 8), wherein the PARP inhibitor is Talazoparib (pg. 2, para 3: BMN673 (talazoparib), a potent trapping PARPi).

Claims 15-17, 24-27, 32-34, 37-38 and 41-42 lack an inventive step under PCT Article 33(3) as being obvious over Sun.

Regarding Claim 15, Sun discloses the method of claim 1 (pg. 1, abstract), but does not disclose wherein the PARP inhibitor is administered to the subject prior to the MAPK activator being administered to the subject. However, it would have been obvious to one with skill in the art to utilize the method disclosed and administer disclosed active agents according to various schedules of administration, as determined upon completion of clinical trials, in order to develop improved methods of treatment.

Regarding Claim 16, Sun discloses the method of claim 1 (pg. 1, abstract), but does not disclose wherein the PARP inhibitor is administered to the subject after the MAPK activator being administered to the subject. However, it would have been obvious to one with skill in the art to utilize the method disclosed and administer disclosed active agents according to various schedules of administration, as determined upon completion of clinical trials, in order to develop improved methods of treatment.

Regarding Claim 17, Sun discloses the method of claim 1 (pg. 1, abstract), wherein the subject is administered a dose of the PARP inhibitor of 0.333 mg/kg per day (pg. 14, Fig. 8: BMN673 (0.333 mg/kg per day)), but does not disclose that is about or less than 960 mg, 720 mg, 480 mg, 240 mg, 150 mg, 100 mg, 50 mg, or 25 mg twice daily. However, it would have been obvious to one with skill in the art to utilize the method disclosed and administer disclosed active agents according to various dosages, as determined upon completion of clinical trials, in order to develop improved methods of treatment.

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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:

Claim 22 is improperly dependent on claim 23 as it further defines a tumor size; for the purpose of this ISR, claim 22 is assumed to depend from claim 21.

Claim 25 is improperly dependent on claim 26 as it further defines a method; for the purpose of this ISR, claim 25 is assumed to depend from claim 24.

Claim 27 is improperly dependent on claim 28 as it further defines a method; for the purpose of this ISR, claim 27 is assumed to depend from claim 26.

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
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Regarding Claim 24, Sun discloses a method of treating a tumor in a subject (pg. 1, abstract: in patients with RAS mutant tumors) comprising administering (pg. 14, Fig. 8: injected into athymic nude mice subcutaneously) to the subject a PARP inhibitor and a MAPK activator (pg. 1, abstract: Synergistic activity of PARP and MEK inhibitor combinations) (MEK inhibitors are MAPK activators as evidenced by instant specification, para [0028]), but does not disclose a solid tumor without a BRAF V600E or V600K mutation. It would have been obvious to one with skill in the art to utilize the method disclosed in order to treat various tumor types, such as those without specific mutations such as BRAF V600E or V600K; through routine experimentation in order to identify optimal use of the disclosed cancer treatment.

Regarding Claim 25, Sun discloses a method similar to the method of claim 24 (pg. 1, abstract), and further discloses wherein the tumor has a genotype of a mutated RAS gene (pg. 1, abstract: in patients with RAS mutant tumors).

Regarding Claim 26, Sun discloses a method of treating a tumor in a subject (pg. 1, abstract: in patients with RAS mutant tumors) comprising administering (pg. 14, Fig. 8: injected into athymic nude mice subcutaneously) to the subject a PARP inhibitor and a MAPK activator (pg. 1, abstract: Synergistic activity of PARP and MEK inhibitor combinations) (MEK inhibitors are MAPK activators as evidenced by instant specification, para [0028]), but does not disclose a metastatic solid tumor without a BRAF V600E or V600K mutation. It would have been obvious to one with skill in the art to utilize the method disclosed in order to treat various tumor types, such as those without specific mutations such as BRAF V600E or V600K; through routine experimentation in order to identify optimal use of the disclosed cancer treatment.

Regarding Claim 27, Sun discloses a method similar to the method of claim 26 (pg. 1, abstract), and further discloses wherein the tumor has a genotype of a mutated RAS gene (pg. 1, abstract: in patients with RAS mutant tumors).

Regarding Claim 32, Sun discloses a pharmaceutical composition for treating a tumor (pg. 1, abstract: in patients with RAS mutant tumors) comprising a PARP inhibitor and a MAPK activator (pg. 14, Fig. 8: vehicle (0.5% hydroxypropylmethylcellulose and 0.2% Tween 80), ... the combination of BMN673 and GSK1120212B) (GSK1120212B is a MEK inhibitor, (pg. 2, para 1: GSK1120212B (MEKi)); BMN673 is a PARP inhibitor (pg. 2, para 3: BMN673 (talazoparib), a potent trapping PARPi)) (MEK inhibitors are MAPK activators as evidenced by instant specification, para [0028]), but does not disclose a solid tumor without a BRAF V600E or V600K mutation. It would have been obvious to one with skill in the art to utilize the composition disclosed in order to treat various tumor types, such as those solid tumors without specific mutations such as BRAF V600E or V600K; through routine experimentation in order to identify optimal use of the disclosed cancer treatment.

Regarding Claim 33, Sun discloses a composition similar to the composition of claim 32 (pg. 1, abstract), and further discloses wherein the solid tumor has a mutant RAS (pg. 1, abstract: in patients with RAS mutant tumors).

Regarding Claim 34, Sun discloses a composition similar to the composition of claims 32-33, as disclosed above, and further discloses wherein the PARP inhibitor is Talazoparib (pg. 2, para 3: BMN673 (talazoparib), a potent trapping PARPi).

Regarding Claim 37, Sun discloses a pharmaceutical composition for treating a tumor (pg. 1, abstract: in patients with RAS mutant tumors) comprising a PARP inhibitor and a MAPK activator (pg. 14, Fig. 8: vehicle (0.5% hydroxypropylmethylcellulose and 0.2% Tween 80), ... the combination of BMN673 and GSK1120212B) (GSK1120212B is a MEK inhibitor, (pg. 2, para 1: GSK1120212B (MEKi)); BMN673 is a PARP inhibitor (pg. 2, para 3: BMN673 (talazoparib), a potent trapping PARPi)) (MEK inhibitors are MAPK activators as evidenced by instant specification, para [0028]), but does not disclose a fixed unit dosage form thereof. However, it would have been obvious to one with skill in the art to prepare a fixed unit dose comprising the disclosed active agents upon completion of clinical trials in order to deliver an optimal dosage thereof.

Regarding Claim 38, Sun discloses a dosage form similar to the fixed unit dosage form of claim 37, (pg. 1, abstract), and further discloses wherein the PARP inhibitor is Talazoparib (pg. 2, para 3: BMN673 (talazoparib), a potent trapping PARPi).

Regarding Claim 41, Sun discloses the use of a PARP inhibitor and a MAPK activator (pg. 1, abstract: Synergistic activity of PARP and MEK inhibitor combinations) (MEK inhibitors are MAPK activators as evidenced by instant specification, para [0028]) for treating a tumor in a subject (pg. 1, abstract: in patients with RAS mutant tumors), but does not disclose treating a solid tumor in a subject, wherein the tumor does not have a BRAF mutation, such as V600E or V600K. It would have been obvious to one with skill in the art to utilize the treatment disclosed in order to treat various tumor types, such as those solid tumors without specific mutations such as BRAF V600E or V600K; through routine experimentation in order to identify optimal use of the disclosed cancer treatment.

Regarding Claim 42, Sun discloses a use similar to the use of claim 41 (pg. 1, abstract), and further discloses wherein the solid tumor is tumor is breast cancer (pg. 2, left col, para 3: breast...cell lines).

Claims 30 and 39 lack an inventive step under PCT Article 33(3) as being obvious over Sun in view of a document entitled "Discovery of RAF265: A Potent mut-B-RAF Inhibitor for the Treatment of Metastatic Melanoma" to Williams et al. (hereinafter Williams).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
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Regarding Claim 30, Sun discloses the pharmaceutical composition of claims 28-29, as disclosed above, and further discloses wherein said composition is utilized to treat BRAF mutant tumors (pg. 13, right col, para 1: BRAF mutant tumors are highly sensitive to PARPi and MEKi), but does not disclose wherein the MAPK activator is RAF265. However, Williams discloses wherein the MAPK pathway comprises RAS/RAF/MEK/ERK and wherein RAF265 is a BRAF inhibitor (pg. 961, left col, para 2: RAF265 (1), a potent inhibitor of B-RAFV600E) for use in treating tumors with a BRAF mutation (pg. 961, left col, para 1). It would have been obvious to one with skill in the art to prepare compositions similar to the composition disclosed by Sun, comprising various inhibitors utilized to treat BRAF mutant tumors which correspond to the same target pathway (MAPK), such as RAF265, as disclosed by Williams; in order to develop synergistic cancer treatment.

Regarding Claim 39, Sun discloses a unit dose similar to the fixed unit dosage form of claims 37-38, as disclosed above, and further discloses wherein said composition is utilized to treat BRAF mutant tumors (pg. 13, right col, para 1: BRAF mutant tumors are highly sensitive to PARPi and MEKi), but does not disclose wherein the MAPK activator is RAF265. However, Williams discloses wherein the MAPK pathway comprises RAS/RAF/MEK/ERK and wherein RAF265 is a BRAF inhibitor (pg. 961, left col, para 2: RAF265 (1), a potent inhibitor of B-RAFV600E) for use in treating tumors with a BRAF mutation (pg. 961, left col, para 1). It would have been obvious to one with skill in the art to prepare fixed unit dosages similar to the composition disclosed by Sun, comprising various inhibitors utilized to treat BRAF mutant tumors which correspond to the same target pathway (MAPK), such as RAF265, as disclosed by Williams; in order to develop synergistic cancer treatment.

Claim 9 lacks an inventive step under PCT Article 33(3) as being obvious over Sun in view of Williams in further view of a document entitled "Stereospecific PARP Trapping by BMN 673 and Comparison with Olaparib and Rucaparib" to Murai et al. (hereinafter Murai).

Regarding Claim 9, Sun discloses the method of claim 1 (pg. 1, abstract), and further discloses wherein said composition is utilized to treat BRAF mutant tumors (pg. 13, right col, para 1: BRAF mutant tumors are highly sensitive to PARPi and MEKi) wherein the PARP inhibitor is talazoparib (BMN673) (pg. 2, para 3: BMN673 (talazoparib), a potent trapping PARPi), but does not disclose wherein the PARP inhibitor is rucaparib and the MAPK activator is RAF265. However, Williams discloses wherein the MAPK pathway comprises RAS/RAF/MEK/ERK and wherein RAF265 is a BRAF inhibitor (pg. 961, left col, para 2: RAF265 (1), a potent inhibitor of B-RAFV600E) for use in treating tumors with a BRAF mutation (pg. 961, left col, para 1). It would have been obvious to one with skill in the art to utilize the method disclosed by Sun, comprising various inhibitors utilized to treat BRAF mutant tumors which correspond to the same target pathway (MAPK), such as RAF265, as disclosed by Williams; in order to develop synergistic cancer treatment. Additionally, Murai discloses comparative studies of PARP inhibitors comprising talazoparib (BMN673) and rucaparib (pg. 433, abstract). It would have been obvious to one with skill in the art to utilize the method disclosed by Sun in view of Williams, comprising similar PARP inhibitors to talazoparib (BMN673), such as rucaparib, as disclosed by Murai, through routine experimentation, in order to develop synergistic cancer treatment.

Claims 1-4, 9, 14-17, 23-30, 32-34, 37-39 and 41-42 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.