PATENT COOPERATION TREATY **TRANSLATION**

From the INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	**19 March 2018**
Applicant's or agent's file reference **P0221712004**	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CN2017/119360	**28 December 2017**	**30 December 2016**

International Patent Classification (IPC) or both national classification and IPC
A61K 31/7068(2006.01)i; A61K 31/4412(2006.01)i; A61K 31/53(2006.01)i; A61P 35/00(2006.01)i

Applicant **CHEN, Xiaohua**

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/	Date of completion of this opinion	Authorized officer

TRANSLATION

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2017/119360

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
   - [x] 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 filed or furnished:
   a. (means)
      - [ ] on paper
      - [ ] in electronic form
   b. (time)
      - [ ] in the international application as filed
      - [ ] together with the international application in electronic form
      - [ ] subsequently to this Authority for the purposes of search

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 in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

TRANSLATION

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2017/119360

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:

[1] Upon verification, the priority claim is established.

TRANSLATION

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2017/119360

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	1-9	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-9	NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims	None	NO

2. Citations and explanations :

[1] Reference is made to the following documents:

[2] Document 1 (D1): CN 101068549 A

[3] Document 2 (D2): CN 105726567 A

[4] D1 relates to a method for treating cancer, as well as a composition and preparation used in the method, which may improve the anti-tumor effect of 5-fluorouracil (5-FU) and a 5-FU prodrug. The preparation comprises a dihydropyrimidine dehydrogenase (DPD) inhibitor and 5-FU or a 5-FU prodrug (see description, page 10, first paragraph and second paragraph from the bottom), wherein the DPD inhibitor may be a reversible or irreversible inhibitor of the DPD enzyme, comprising CDHP, and the like, and the 5-FU prodrug is preferably capecitabine (see description, page 13, paragraph 2, and page 20, paragraph 1).

[5] D2 relates to an oral chemotherapy tablet for the treatment of gastric cancer, which is made of capecitabine, a cisplatin liposome and oteracil potassium; the capecitabine may be become 5-FU within the body, which allows more 5-FU to be concentrated within gastric tumor cells, while oteracil potassium has a high distribution concentration in gastrointestinal tissue, affecting the distribution of 5-Fu in the gastrointestinal tract, and thereby reducing the toxicity of 5-Fu (see description, paragraphs [0006]-[0009]).

[6] I. Novelty

[7] Neither D1 nor D2 discloses a pharmaceutical composition or kit comprising capecitabine, gimeracil and potassium oxonate. Thus, claims 1-9 are novel and comply with PCT Article 33(2).

[8] II. Inventive Step

[9] D1 is the closest prior art document, and discloses a preparation for treating cancer that comprises a DPD inhibitor and a 5-FU prodrug, wherein the DPD inhibitor may be CDHP (equivalent to gimeracil), and the 5-FU prodrug may be capecitabine. On the basis of the foregoing, a person skilled in the art would be motivated to prepare an effective amount of capecitabine and gimeracil into a pharmaceutical composition or a pharmaceutical kit. Meanwhile, under the motivation of D2, a person skilled in the art could easily conceive of adding oteracil potassium (equivalent to potassium oxonate) into the described composition or kit so as to reduce the side effects of capecitabine. Therefore, claims 1, 6 and 9 do not involve an inventive step and do not comply with PCT Article 33(3). Meanwhile, selecting a pharmaceutically acceptable salt of gimeracil, or an acid-addition salt or a salt of a basic compound of potassium oxonate is a common option for a person skilled in the art, and the molar ratio of the three components may be determined by screening by means of conventional experiments. Therefore, claims 2-5, 7 and 8 do not involve an inventive step, and thus do not comply with PCT Article 33(3).

[10] III. Industrial Applicability

[11] The technical solutions of claims 1-9 can be applied in the pharmaceutical industry, and thus said claims comply with PCT Article 33(4).