

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.
PCT/IB2023/056844

International filing date (day/month/year)
30.06.2023

Priority date (day/month/year)
05.07.2022

International Patent Classification (IPC) or both national classification and IPC
INV. A61P35/00 C07D519/00 A61K31/55

Applicant
PFIZER INC.

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 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:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Hanisch, Inken

Telephone No. -0



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 43bis.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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
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 43bis.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 43bis.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:

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

1. Statement

Novelty (N)	Yes: Claims	<u>1-32</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-32</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-32</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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

Re Item V.

Reference is made to the following documents:

- D1 FELL JAY B. ET AL: "Identification of the Clinical Development Candidate MRTX849, a Covalent KRASG12C Inhibitor for the Treatment of Cancer", JOURNAL OF MEDICINAL CHEMISTRY, vol. 63, no. 13, 6 April 2020 (2020-04-06), pages 6679-6693, XP055788094, US
ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.9b02052
Retrieved from the Internet:
URL:<http://pubs.acs.org/doi/pdf/10.1021/acs.jmedchem.9b02052>
- D2 WO 2022/132200 A1 (MIRATI THERAPEUTICS INC [US]) 23 June 2022

Claims 21-24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Novelty

The compounds of current formulae (V) and (VII) as claimed in current claims 1 and 16 as well as those specific compounds not falling within either general formula claimed in current claim 19 are considered to be novel over D1 and D2: They essentially differ from said prior art due to their (optionally further fused) seven- or eight-membered heterocycle fused to the pyridopyrimidine bicycle. By consequence, all claims are novel over D1 and D2.

Inventive Step

Both D1 and D2 disclose pyridopyrimidine derivatives which have anticancer activity due to their KRASG12C/Pan-KRAS inhibiting ability (see e.g. D1 abstract, D2 table 5 on page 725) and can be considered to be the closest prior art.

Currently claimed compounds of formula (V) as well as the additional compounds claimed in independent claim 19 have been shown to inhibit KRAS G12C, KRAS G12D and KRAS G12V (see table 3 on current page 101: compounds 27 and 33 re formula (V) as well as compounds 23, 24, 26, 29, 31 and 32 re current claim 19, see also item VIII below). They essentially differ from the disclosure of D1 and D2 due to their at least one seven- or eight-membered heterocycle as claimed being peri-fused to the pyridopyrimidine core. The skilled person looking for further anticancer agents which are able to inhibit at least KRASG12C had no incentive to arrive at the current solution from either of D1 or D2. As a consequence, the current solution is considered to be non-obvious over D1 and D2.

Re Item VI.

Certain documents cited

Certain published documents

Application No	Publication date	Filing date	Priority date
WO 2023/ 046135 A1 (D3)	30-03-2023	26-09-2022	27-09-2021
			18-03-2022
			29-06-2022
			21-09-2022
WO 2022/199587 A1 (D4)	29-09-2022	22-03-2022	24-03-2021
			18-09-2021
			28-01-2022
			25-02-2022

D3 which has been filed in-between the currently claimed second and third priority dates (of 21-08-2022 and 11-10-2022, respectively) has been published in-between the currently claimed third and fourth priority (of 11-10-2022 and 18-05-2023, respectively) and claims three priority dates which are earlier than the currently claimed earliest priority date (of 05-07-2022). D3, which discloses general formulae and specific

compounds of the desired activity anticipating current subject-matter (see in particular the claims and compounds 1-6, 9, 13, 15, 19, 23 and 24 of D3), may thus become relevant for novelty at least involving all of its subject-matter entitled to one of its first three priority dates (of D3) as well as for all current subject-matter not entitled to one of the first two currently claimed priority dates. Furthermore, D3 may be considered to be highly relevant for inventive step for all current subject-matter not entitled to one of the first three currently claimed priority dates.

D4 which has been filed prior to the currently claimed earliest priority date (of 05-07-2022) and published in-between the currently claimed second and third priority dates (of 21-08-2022 and 11-10-2022, respectively) is considered to disclose subject-matter which could be relevant for the assessment of inventive step at least for those current compounds which are not entitled to one of the first two currently claimed priority dates, and which are considered to be a novel selection from the disclosure of claim 1 of D4, having the same activity.

Re Item VII.

Current claims 22 and 23 are drafted as independent claims, however, their subject-matter is considered to fall within the scope of current claim 21.

It is noted that the description contains incorporations by reference (see p.103) and a passage relating to the spirit of the invention (see p.103).

Re Item VIII.

Claim 19 contains one specific compound which is considered to fall within the scope of current claim 1, see the first compound in line 2 of compounds, i.e. current compound 27. In order to avoid casting any doubt on the scope of protection sought this compound should not be subject of an independent claim but of a dependent claim.

The scope of current claim 30 is considered not to be clearly defined as the therapeutic application of the molecules is functionally defined by a mechanism of action (i.e. by their capability of inhibiting KRAS G12C, KRAS G12D and KRAS G12V receptors), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

The scope of the invention needs to be clearly defined by the claims and them to be fully supported by the description (Article 6 PCT). In this respect, two issues are noted:

- First, the description contains subject-matter much broader than what is claimed, see e.g. formulae (I)-(IV), embodiments E1-E62 and corresponding examples, as well as prodrugs or metabolites (see e.g. pages 36, 37) and as such casts doubts on the scope of the actual invention. This opinion exclusively relates to the subject-matter currently claimed.
- Second, current claim 31 appears to lack a true counterpart in the description. It is noted that it differs from embodiment E93 (see current page 25).