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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:

10 November 2022 (10.11.2022)

(54) Title: HER2/4-1BB BISPECIFIC FUSION PROTEINS FOR THE TREATMENT OF CANCER

(57) Abstract: The disclosure provides methods and compositions for treating tumors, particularly HER2-expressing tumors. The method comprises administering a therapeutically effective amount of a HER2/4-1BB bispecific fusion protein. The HER2/4-1BB bispecific fusion protein may be administered at a first dose and, subsequently, at a second dose, wherein the first dose exceeds the second dose.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER INV. A61K38/00 A61P35/00 A61K39/00 C07K16/28 A61K47/68 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61P A61K C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/043683 A1 (PIERIS PHARMACEUTICALS GMBH [DE]) 5 March 2020 (2020-03-05) cited in the application the whole document -----	1-31
X	KU G. ET AL: "5250 A phase I dose escalation study of PRS-343, a HER2/4-1BB bispecific molecule, in patients with HER2-positive malignancies", ANNALS OF ONCOLOGY, vol. 31, 1 September 2020 (2020-09-01), pages S462-S463, XP055943681, NL ISSN: 0923-7534, DOI: 10.1016/j.annonc.2020.08.639 Results and Conclusions ----- -/--	1-31
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
18 July 2022		23/09/2022
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Steinheimer, K

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International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARLON J. HINNER ET AL: "Tumor-Localized Costimulatory T-Cell Engagement by the 4-1BB/HER2 Bispecific Antibody-Anticalin Fusion PRS-343", CLINICAL CANCER RESEARCH, vol. 25, no. 19, 28 May 2019 (2019-05-28), pages 5878-5889, XP055708423, US ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-18-3654 page 5885 - page 5887 -----	1-31
Y	ANDREAS LUNDQVIST ET AL: "31st Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer (SITC 2016): part one : National Harbor, MD, USA. 9-13 November 2016", JOURNAL FOR IMMUNOTHERAPY OF CANCER, vol. 4, no. S1, 1 November 2016 (2016-11-01), XP055743746, DOI: 10.1186/s40425-016-0172-7 the whole document -----	1-31
Y	WO 2018/140831 A2 (SILVERBACK THERAPEUTICS INC [US]) 2 August 2018 (2018-08-02) paragraph [0584] -----	1-31
Y	WO 2020/208049 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 15 October 2020 (2020-10-15) the whole document -----	1-31
Y	WO 2019/197600 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 17 October 2019 (2019-10-17) the whole document -----	1-31

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out 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 13ter.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 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ 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.
3. Additional comments:

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

1-31

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-31

Fusion protein that comprises an antibody specific for HER2 fused at the C-terminus of both heavy chains to the N-terminus of a lipocalin mutein specific for 4-1 BB as defined in claim 1, for use in treating a HER2-expressing tumor by using a dosing regimen as defined in claim 1.

2. claims: 32-45

A fusion protein that comprises an antibody specific for HER2 fused at the C-terminus of both heavy chains to the N-terminus of a lipocalin mutein specific for 4-1 BB as defined in claim 32 for use in treating a tumor in a subject, wherein the tumor is characterized by a low expression of HER2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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